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Curriculum Units by Fellows of the National Initiative
2011 Volume VII: Organs and Artificial Organs

Your Liver, Can It Survive Your Abuse?

Curriculum Unit 11.07.12, published September 2011
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Rationale

Liver, Liver, Liver. No matter how you say it, it does not sound exciting or melodious. Liver is the most ignored of our major organs. Why? People know a bit about the heart, kidneys, digestive system, sexual organs, sometimes the pancreas and even the gall bladder, but the second largest organ in our body (after skin) is ignored. It is the only organ that receives blood from both the heart and another organ. It is involved in many vital functions in the body. It can regenerate and be transplanted, yet cannot be cultured. All of its cells are almost the same, but it performs more functions than any other organ. Why do physiologists and educators find it so unmemorable? Why when I talk about liver do people think I said kidney? This may be because it is so complex and involved in so many bodily functions. It is part of glucose regulation, cholesterol regulation, digestion of fats, storage of vitamins, is an endocrine and an exocrine gland, stores minerals and detoxifies poisons. Yet, it never gets its own chapter in physiology books and is instead scattered throughout the various systems it can be classified with, such as digestive, exocrine, and endocrine systems.

I teach in a small high school of approximately six hundred students in northern California, just south of San Francisco. We have a diverse population. There is not a majority of any ethnic group. The largest minority population is Filipino. Next largest is Caucasian, then Latino. We have several other groups represented as well, African American, Chinese, Japanese, Thai, Indian, Tongan are some of the ethnic groups.

Because of the culture of many of our immigrants and first generation Americans, we have a lower alcohol consumption compared to other high schools in the area. We have approximately the same rate of marijuana use, however. We also have comparable amounts of illegal drugs of abuse, over the counter drugs (OTC), and prescription drug abuse.

I teach health to our students and an important part of my curriculum is education about drug abuse, including tobacco, alcohol, illegal drugs, and prescription and OTC drugs. I have found that the students are quite tired of the messages they have received about illegal drugs of abuse throughout elementary and middle school based on the infamous "just say no" approach. They can recite side effects of tobacco, alcohol and illegal drugs, but do not believe them. Teachers have sometimes exaggerated these side effects to the point where it contradicts the reality the students see. Also, they do not understand that readily available medications are also drugs and have side effects, some of which are deadly. While I cannot combat all of their boredom with drug education, I can give them specifics about why the various drugs they have learned about

are unsafe; I can explain that prescription and OTC medications are drugs; I can emphasize that all drugs have side effects. They also must be aware that drugs like acetaminophen are found in multiple OTC products and it is possible to accidentally overdose by taking several cold or flu symptom relievers. To be informed medical consumers, they must read labels and realize whether or not they are taking drugs that have a cumulative effect. They need to understand that an important job of both themselves and their doctor is to decide if the benefits outweigh the negative effects of the drugs they take. The liver, because it is the organ responsible for converting most drugs to inactive forms, and because it is the organ responsible for elimination of many drugs, is often the first organ to be damaged when drugs are abused.

Introduction

The unit will start with an introduction on why we are studying the liver, especially as regards drug use. Students will learn about liver structure, focusing on organization as it relates to function. We will start with the liver's microscopic organization, understanding the hexagonal organization of the liver cells and the proximity to hepatic artery, hepatic vein, portal vein and bile duct. This will lead to macroscopic organization, with the dual circulatory system and other unique characteristics of the liver. We will learn about the many, many functions of the liver, especially its role in detoxifying drugs and poisons that are inadvertently taken into the body. We will need to touch on most of its functions to emphasize the importance of having a functioning liver.

I want students to learn some specific effects of drugs and disease on the liver. I will concentrate on Hepatitis B, a sexually transmitted disease studied during sex education; Hepatitis C, which can be sexually transmitted, but is more often acquired from risky behavior, such as needle sharing; and acetaminophen, which is a common over the counter (OTC) drug, often added to other OTC medications to make them more effective, and a cause of acute liver failure. I will briefly touch on mushrooms as a warning to avoid eating them if they were not grown or picked by an expert. We will brainstorm and attempt to design an artificial liver that can take over some of the functions that disease and drugs can interfere with. Finally, we will look at liver transplants and spend time discussing the ethics of transplant, including who should get them. Should it make a difference how you damaged your liver? Is ongoing risky behavior an issue? Who should pay for the transplant? Is it right for it to be only available to the rich? What is the role of insurance companies in deciding who get treated? These are rich, in depth questions that will hopefully open the opportunity for my students to question things that they currently accept as givens. I believe it will be a more interesting approach to a topic they have heard every year that they have attended school.

Background

Structure

Liver cells (also called hepatocytes) are arranged in hexagonal units, an arrangement that allows them to fit together tightly, yet still have contact with three parts of the circulatory system and the bile duct (figure 1). In the center of each hexagonal unit is a branch of the hepatic vein, which goes back to the heart. At each of the

six corners of the hexagon is a bundle of three tubules. One is a branch of the hepatic artery, bringing nutrients, oxygen and other chemicals needed by the hepatic cells. The second tubule is a branch of the portal vein, carrying nutrients and drugs directly from the digestive system to the liver cells. The third is a branch of the bile duct. Cells are arranged in a hexagonal fashion, with the central or hepatic venule centralized in each hexagonal unit. Triad bundles are found at each hexagonal corner. In the bundles are a hepatic arteriole, a portal venule and a branch of the bile duct(see figure 1). Bile is produced by the liver and excreted into the bile duct system and is important in fat metabolism. It makes fat soluble, so it can be transported as a fluid. Bile can be stored in the gall bladder, prior to its elimination through the digestive system. The bile system provides a pathway that is often used to eliminate drugs or the breakdown products of drugs, which can also be fat soluble, from the liver. A chemical can be absorbed by the hepatocytes and excreted directly into branches of the bile duct. From there, it can be excreted into the intestines and eliminated from the body. Another way the liver detoxifies chemicals is by converting them into metabolites, which are more easily excreted by the kidneys or intestines.

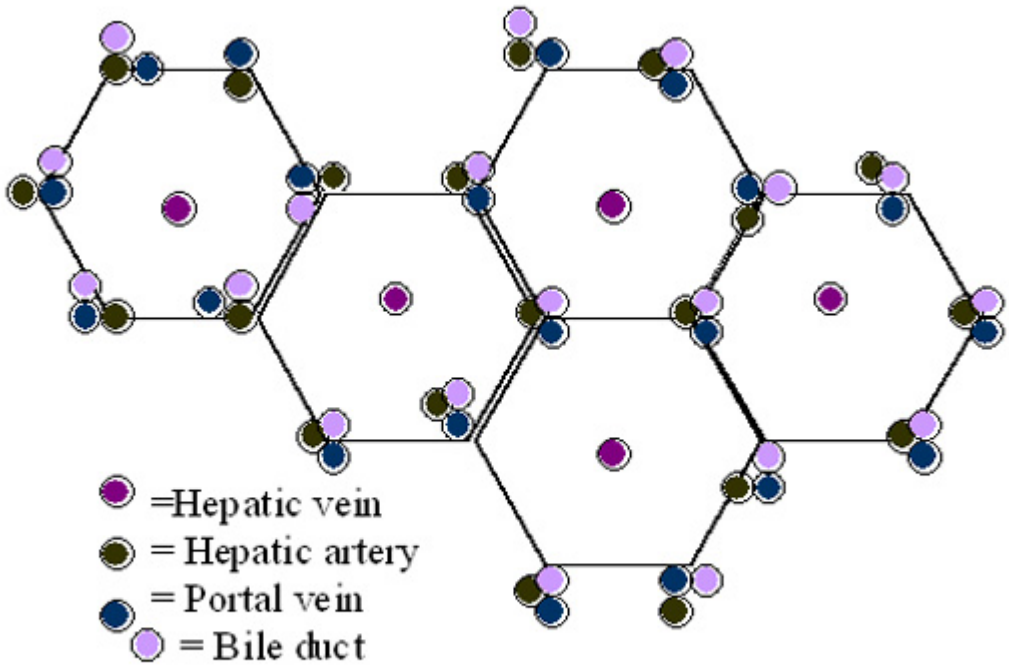

Fig 1

The bundle of three tubules at each corner of the hexagonal hepatocytes plus the central hepatic vein constitute the functional parts of the blood and bile circulation, which are intimately connected to the liver. In general, the circulatory system is straightforward. Blood goes from the heart to the lungs with a high percentage of carbon dioxide and comes back to the heart with a high percentage of oxygen. It then goes out to the various organs with oxygen and comes back to the heart with more carbon dioxide again. Circulation through the systemic and pulmonary vessels can be compared to a figure eight with the heart at the intersection. The liver adds some complexity to that system. It receives oxygenated blood from the heart through the hepatic artery. It also receives deoxygenated blood from the intestines through the portal vein. This blood is rich in nutrients and toxins and goes through the liver before going to the rest of the body. The liver is the only organ that receives multiple circulatory systems, which is a measure of its importance.

Functions

The liver works as a blood filter. It contains a high proportion of phagocytic cells, (Kuppfer cells). These are macrophages, a type of white blood cell, which go into and out of the circulatory system. Most of them are found in tissues, prowling for foreign objects to destroy. It is estimated that most of the fixed macrophages in the body are the Kuppfer cells in the liver. Because so much of the blood supply is shunted through the liver, the Kuppfer cells have the opportunity to phagocytize many foreign particles. For example, Kuppfer cells in the liver routinely scavenge old red blood cells, the main solid component of blood and our transport mechanism for oxygen. The actual transport protein for oxygen is hemoglobin, which contains iron. As the liver breaks down the red blood cells, the proteins are also digested for reuse of the components. To do this safely, the iron molecules that are released then have to be stored for reuse in a non-toxic form. The iron is generally coupled with ferritin to protect the cells in the liver from toxic effects of iron. Kuppfer cells can also phagocytize bacteria, small parasites, and circulating toxins.

The liver is important in detoxifying poisons. As previously mentioned, the toxins can be exported from the liver to the intestines through the bile duct. Usually, toxins are metabolized to a more soluble form. Sometimes they are metabolized by the hepatocytes and then sent into the venous circulation, where they are filtered by the kidneys for excretion. Urea is made by the liver and travels to the kidneys for concentration and excretion. Urea is especially high in nitrogen, a component of amino acids, which the liver cells digest. Liver cells package the excess nitrogen into urea, which can be excreted.

One of the toxins produced by breakdown of the hemoglobin, the oxygen carrying protein in red blood cells, is bilirubin. Macrophages phagocytize old red blood cells, breaking down the hemoglobin and releasing free bilirubin into the blood that is then bound to albumin. Hepatocytes take in the bilirubin that is loosely bound to albumin. Within the liver cell, bilirubin is conjugated with glucuronic acid. In this form, it is soluble and can be released into bile. Increased levels of bilirubin cause jaundice. Jaundice is the yellowing of skin and eyes that is an external indicator of major liver damage. The levels of both conjugated and unconjugated bilirubin can be informative of what kind of liver disease a patient has.

The hepatocytes are also involved with breaking down nutrients. They are especially important in the digestion of fats. Hepatocytes make bile, the main function of which is to make fats soluble in blood. The cells of the body can then absorb the fats for nutrition. Bile is also an excretory route for various metabolites of toxins. Bile contains bile salts, bilirubin, cholesterol and other compounds. These compounds can be concentrated and stored in the gall bladder. Bile helps maintain body cholesterol levels through control of its excretion rate. It is part of the mechanism for excreting heavy metals. Many of the contents of bile secreted by cells are reabsorbed and recycled to the liver and gallbladder.

One of the most important roles of the hepatocytes is to aid in the control of the blood sugar. We always think of the pancreas controlling blood sugar through insulin, but, in fact, the liver also plays a major role. The liver stores glycogen, a polymer of glucose molecules, which can be digested for release into the bloodstream when glucose levels are low. Glucose is the simple sugar that cells use for energy. The liver is involved in the feedback system controlling the amount of glucose in the blood. Blood levels must remain relatively constant, because glucose must be kept at a level necessary for proper brain cell function. Once the glucose level goes down too far, the brain cells start dying. Insulin, when secreted by the pancreas, lowers the glucose concentration, but the liver is a major site of action for insulin, and it is the key to not letting blood sugar get too low (figure 2). Hepatocytes are also capable of gluconeogenesis, making glucose by converting amino acids and simple sugars to glucose. Other cells can only break down glycogen (or other complex forms of

glucose polymers) into glucose. The liver can actually transform other molecules into glucose.

Figure 2 is a simple flowchart showing the regulation of blood glucose by fat, muscle, and liver cells, which is orchestrated through insulin and glucagon. After a meal, the flow chart on the left shows that the blood glucose goes up, causing increased insulin secretion by the pancreas. Insulin acts on fat, muscle and liver cells to take up more glucose. Glycogen synthesis from glucose is increased in the liver and muscle cells and glucose synthesis via gluconeogenesis in decreased in the liver. These actions result in a decrease in blood glucose level. The flow chart on the right shows the opposing actions during low blood sugar, as in before a meal. Low blood glucose increases glucagon secretion by the pancreas, targeting the liver. In the liver, this causes increased glycogen breakdown into glucose and also increased gluconeogenesis. The pancreas decreases insulin secretion, all acting together to increase blood glucose.

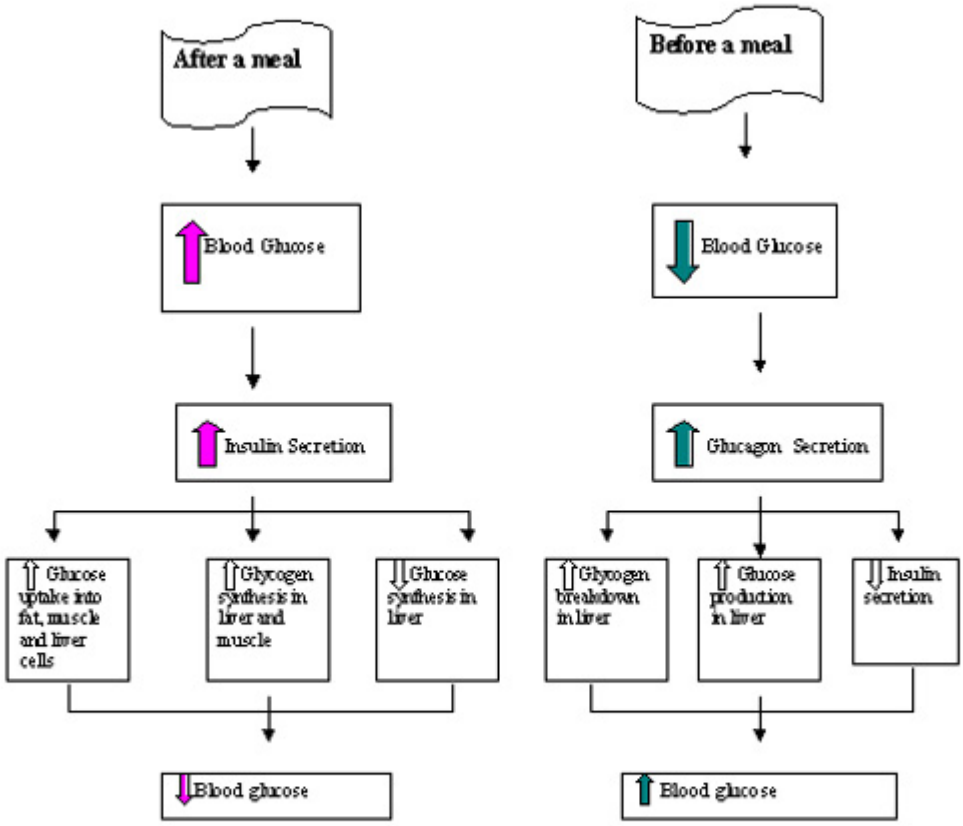

Fig. 2

The liver is also important in the production of cholesterol, a fat that all of the cells in the body need. Cholesterol is absolutely essential for the healthy function of cell membranes; it is also the starting chemical for the synthesis of steroids and vitamin D. It is important in protecting the skin from water or evaporation, and forms the sheath around nerve cells, which aids in the signal going all the way to the end of the axon, especially very long ones. It is not broken down for energy. As was previously mentioned, excess cholesterol is excreted in bile. When we talk about "good" cholesterol vs. "bad" cholesterol, in general, the liver makes much of the good cholesterol and much of the bad cholesterol is from food sources, specifically from animals. It is not found in plants.

Fat-soluble vitamins are metabolized and stored in the liver. As mentioned above, the liver uses cholesterol to make Vitamin D, which has been considered a fat-soluble vitamin for many years. But, biochemists are currently classifying it as a hormone. Vitamin D is also stored in the liver. Vitamin D is necessary for absorption of calcium. Vitamins A, E and K are all metabolized and stored in the liver. All are necessary for the health of humans in various ways. Vitamin A is part of the pathway the eye uses in adapting to low light, i.e. night vision. Vitamin E is an antioxidant, probably preventing oxidation of unsaturated fatty acids. Vitamin K is used in the clotting of blood, along with fibrinogen, a protein made by the liver, coagulation factors, and platelets.

The liver is responsible for several other important jobs. Copper is stored in the liver. Many important proteins are synthesized by the hepatocytes, such as albumin, carriage proteins (that bind and transport hormones and other substances) and coagulation factors, important in blood clotting. Coagulation factors are another way to test for liver function, since if it is not producing coagulation factors, the blood does not clot as quickly.

Tests for liver function

There are several laboratory tests for liver function. Two tests, which are generally ordered together, are blood tests for the enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST). These are not specific tests, but are indicators of liver tissue damage and necrosis. Doctors also look at the ratio between them for further information about the site and extent of the damage in the patient Alkaline phosphatase is also a non-specific enzyme that is elevated in liver disease. Elevated bilirubin can also be tested for and indicates liver disease or sometimes a disease causing increased breakdown of red blood cells. Prothrombin time, a test for coagulation of plasma, can also indicate liver disease or damage resulting in a lack of liver produced coagulation factors. Testing for albumin levels is another test. The protein albumin is made only by hepatocytes and is abundant in plasma, so a low level of albumin or even total protein, can be an indicator of liver damage. There are also tests for the viruses that cause hepatitic disease. The florescent monoclonal antibody tests for hepatitis B antibody (HBAB), hepatitis B core antibody (HBc), and hepatitis B surface antigen (HbsAg) have been available for many years. The test for HCV antibody has been available since the nineteen nineties. These are standard immunology tests for hospital labs and in fact are done on all donor blood before it can be transfused, since HBV and HCV are infectious through blood products.

Factors affecting the liver

Many things can affect viability of hepatocytes. In the documentary, SuperSize Me, which is about the effects of processed food on our bodies, the writer/ director/ central character eats only food from a well known fast food restaurant for thirty days. His doctor finds increased liver enzymes (ALT and AST), which are laboratory indicators of liver damage, within two weeks of starting the diet and diagnoses him with fatty liver disease, which can be a life threatening disease leading to cirrhosis and possible death. Since Morgan Spurlock is healthy at the beginning of the thirty days and does not drink alcohol, the obvious culprit is his diet of processed foods. Although this was not a controlled study, there have been many studies examining the negative effects of processed food and so this anecdotal evidence seems to point towards processed food causing the fatty liver. Fatty liver disease is normally found in women with Type II diabetes, who are obese, and/ or have hyperlipemia (high lipid or fat levels) in the blood. The fact that Mr. Spurlock gained almost twenty pounds in the first two weeks of the diet seems to mimic some of the effects that normally cause non-alcoholic fatty liver disease.

Hepatitis B Virus (HBV) is a DNA virus, that is transmitted by exposure to body fluids. In the USA, it is commonly spread through sexual contact, needle sharing, or mother to child during pregnancy or childbirth. It

was a common infection of health care workers until the early to mid-nineteen eighties, when HIV became widespread. At that point universal precautions were put in place and latex gloves and hand washing were required any time there was contact with blood or body fluids. The incidence of new cases of HBV among health care workers dropped dramatically. Severe allergies to latex increased, but that is a different story. An effective vaccine to HBV became available in the early nineteen nineties, soon after universal precautions were required, dropping new infection rates even more.

HBV infection can manifest in three ways. It can be asymptomatic, with the patient not realizing he or she is infected unless tested. It can cause acute liver disease, which usually resolves within six months. And it can become chronic, with the person shedding virus for the rest of his or her life. HBV can be spread during the asymptomatic, but active, disease phase. It is one of the most common sexually transmitted infections (STI's) and protection against spread should be used during sexual activity. The virus targets hepatocytes and causes liver damage, often necrosis (death) of the cells. It can also cause fibrosis, where too many matrix proteins, such as collagen, are produced which replace the liver cells, and eventually cause cirrhosis. Cirrhosis is a build up of scar tissue in the liver, which eventually impedes liver function. The hepatocytes may regenerate, but the intimate contact with blood vessels that is so important for normal liver architecture and function, is lost. When cirrhosis occurs, illness can be caused by the loss of the important substances that the liver produces. The build up of toxins from the bile not being channeled properly can also cause systemic damage. Finally, the role of the liver in glucose regulation can cause great damage to the rest of the body, since the liver plays an essential role in maintaining sufficient glucose in the blood (i.e. brain damage can result from low blood sugar).

Chronic HBV can develop after asymptomatic or acute infection. It can result in long-term damage to the liver. HBV virus in present in the infected person's blood and is constantly shed. The HBV positive person can spread the virus through sexual transmission or blood and may not realize it until there is a reason to screen him or her for hepatitis.

HCV is the virus responsible for most of the viral infections formerly called non-A, non-B hepatitis. It is most commonly spread through shared needles. It is a common infection amongst IV drug abusers. It is also an infection that is frequently spread through tattoos and piercings with a dirty (i.e. reused or improperly sterilized) needle. More than half of people infected with the virus progress to chronic disease. The virus can cause fibrosis and cirrhosis of the liver. It is a more aggressive chronic disease than that caused by HBV. It is the most common reason for liver transplantation. HCV also exacerbates liver damage from other illnesses or drugs.

Many drugs cause liver disease, including acetaminophen, the pain reliever in Tylenol; acetylsalicylic acid, or aspirin; many prescription medications; illegal drugs of abuse; and alcohol abuse. Since OTC drugs are part of the state standards for health and they seem to be misunderstood by almost all of my students, I will focus on acetaminophen.

There is great concern about acetaminophen overdose due to several factors. It is extremely toxic to the liver in high doses. Many people, especially teenagers, consider it safe because it is so freely available. It is added into many OTC and prescription medications, so it is relatively easy to overdose if you are not aware of the ingredients in your medications. OTC cold and flu remedies frequently contain acetaminophen. Often people use the old adage more is better and combine various drugs and/or take them in higher doses than suggested, including taking some Tylenol for their fever. You could potentially take several drugs containing acetaminophen without realizing it, if you do not read the labels carefully. Some people use it for suicide

attempts since it is so readily available, as well.

Acetaminophen is considered an intrinsic hepatotoxic drug due to the frequency of damage done to the liver when the drug is used improperly. People with previous liver damage can be affected even at normal dosage. Alcoholics and people with active cases of HBC or HCV are especially susceptible. It is believed that there are many more cases of drug induced liver damage than are reported. It is difficult to diagnose. The damage is exacerbated by other factors, such as previous liver damage by alcoholism and viral hepatitis. It is also much more damaging in obese and anorexic patients.

Acetaminophen affects the mitochondria within the hepatocytes, causing the mitochondrial membrane to become more permeable, which results in disruption of the cytoplasm and loss of much of the ATP of the cell. The mitochondria, which are small organelles inside each cell in the body, are responsible for the energy production and storage for the cell. They use oxygen and nutrients to convert molecules of ADP to ATP, which uses energy to go from two phosphate groups in each molecule to three. When the ATP is converted back to ADP by removing a phosphate group, energy is released for use by the cell. If the cell has no energy available to make protein or facilitate transfer of necessary molecules into the cell or any of the other millions of jobs it needs to do, it will rapidly die.

Some mushrooms can also cause liver failure. The most frequent cause is *Amanita phalloides*. Generally, the mushroom is eaten accidentally by confusing it with edible mushrooms. It is a good idea not to pick your own mushrooms or eat the ones picked by someone else unless they are known to be an expert. Mushrooms are easily confused. *Amanita* apparently produces a toxin that inhibits RNA polymerase. RNA is vital to all cells, since it is necessary to protein production.

Liver transplants

Transplantation of livers is relatively new. Currently, HCV infection is the number one indicator for transplant. But there are other indications, including liver damage from alcoholism or HBV infection or many other causes. In general, the build up of scar tissue is an indicator for transplant, since the cells regenerated by the liver are blocked from necessary vascularization by the scar tissue. As we have seen, vascularization is extremely important to hepatocytes and each one must be within diffusion distance of a branch of the hepatic vein, a branch of the portal vein from the intestines, a branch of the hepatic artery and a branch of the bile duct. Without all of these, vital chemicals such as cholesterol cannot be manufactured, glucose regulation cannot be done, toxic substances, such as drugs and bile, cannot be excreted.

Transplants can be obtained from a cadaver liver. In that case, because of the regenerative properties of hepatocytes, the liver can be split in two and given to two recipients. Transplant surgeons have also been doing designated liver transplants to patients, usually from a relative or close friend. Since this is a serious operation on the donor, with a lengthy recovery time, there are many steps and safeguards around the procedure. But a partial liver can regenerate in both the donor and recipient. Obviously, if the recipient has an active case of HCV or HBV, this can easily escalate with a new liver to infect. Doctors treat the patients aggressively with antiviral agents. There is no cure, but the disease can be kept under control better. For alcoholics, it is complicated by their addiction. If they go back to drinking large quantities of alcohol, the transplant becomes a temporary solution.

Transplant ethics

We have all seen the movies and read the books about evil organ dealers putting people into a coma and

harvesting their organs to sell to rich people. Sometimes the stories are about immigrants being forced to sell a kidney for protection from deportation. Jodi Picoult wrote a story of a family who deliberately had a second child to provide bone marrow transplants for the first. It examined the issues around whether a person owns their own body. Is it legal for parents to demand that one child give transplants to another? There was a recent governor's decision to free a prisoner if she would donate a kidney. I have a friend with Lupus whose sister donated a kidney. She was happy to do it, but it was a temporary measure and the recovery time for the donor was not easy. How do they decide who gets a transplant, whether it is from a dead donor, as with most transplants, or from a living one, as can be done with livers, kidneys and bone marrow?

Who should donate an organ, specifically a part of the liver? If you have a child dying of liver failure, the impetus to donate could be overwhelming. It seems like a huge commitment from a friend, more distant relative, or a stranger. Liver donation is not a simple thing, it takes time to recover from, it can result in ill health or occasionally even death. Is it ethical to pay someone to donate part of his or her liver for a transplant? Do we want to live in a world where all medical issues are decided by money and big business? It seems like we are headed that way with private insurance companies controlling what procedures are done and not done for those of us without unlimited funds. What about forcing someone to donate? Prisoners have been forced into being experimental subjects in the USA before. Should we value contributing members of society over the non-contributing? (We can analyze our current values system by comparing money spent on schools to money spent on prisons, comparing salaries for working people like plumbers, teachers, waiters, to so-called celebrities, actors, football players, etc.) At what point do we become like Josef Mendel, experimenting without conscience on the mentally and physically disabled, torturing twins to see whether their reactions differ? This may be an exaggerated concern, but it has happened to greater or lesser extent in modern medicine. Even donations from cadavers can be controversial. Some families of donors object strongly to their dead relatives organs being used, even if the donor gave permission when alive. Another controversy would be to harvest organs from brain dead people, keeping them "living" until the organs can be used. Now we keep our dying alive in pain and indignity, would it be worse to do it for a reason besides fear of lawsuits?

In reality in the USA today, most states request drivers to agree to donate organs as an option when they renew their driver's licenses. They are only listed as donors if they take an active step to become one. If their families object to donating organs when the person dies, they override the expressed wishes of the deceased. In our lawsuit happy society, it is deemed better to lose the organs than to take a chance on lawsuits and bad publicity. Organ sales are illegal in the USA, but there is a black market in many countries and wealthy Americans often buy the organs. There have been suggestions that we make selling organs such as kidney, liver and bone marrow legal, with a set price for each organ.

Another difficult problem is deciding who gets the donated organ. Life and death decisions are made since there are never enough organs for the recipients. Physicians have to worry about age and chances of survival. What about whether the recipient deserves one? If an IV drug abuser has HCV, should they get a new liver, having brought on liver disease through their addiction? Would the liver even last? Drug addicts recover so infrequently. Would someone who contracted HCV through getting a tattoo at a party deserve a new liver? Should they be punished for one stupid decision? Should prisoners be placed lower on a list than upstanding citizens? What about someone in prison for marijuana use vs. someone convicted of raping and murdering a child?

In the USA, these issues are mainly decided by doctors who specialize in transplants and by UNOS, a private organization that is contracted by the federal government to maintain all the data on transplants and make the matches based on histological compatibility (so minimizing the chance of organ rejection), the likelihood of

success and the probable length of post surgical life. So, a young, healthy person in need of a transplant would be more likely to be high on the list than an older healthy person, if all other factors are equal. Much of the inequity is found at the first level, the transplant doctors who recommend patients to UNOS. Since their highest priority is getting paid, the wealthy and people with the best medical insurance are likely to be highest on their list of recommendations. Surprisingly, at least to me, prisoners have ready access to transplants, being among the few Americans with free comprehensive health care.

Artificial livers

Replacing a failing organ with an artificial one has been successful in a limited way for many years. Dialysis for kidney patients has been available and has been refined to a simple and effective system. There is a similar system now available to those with liver failure. Blood is removed from the body and returned in a similar manner to dialysis. In this case, blood cells are strained out, separated from the plasma and returned to the body in plasmapheresis, the first step. Plasma is then physically filtered through charcoal to remove relatively large foreign objects. Plasma is then pumped through a hollow-fiber bioreactor, in contact through a membrane with cells outside of it. Pig liver cells are used, since the hepatocytes function similarly to human hepatocytes. Since there is no actual physical contact between the human cells and the pig liver cells, there is no immune reaction. The liver cells are then stimulated to produce the many hormones, proteins, bile, albumin, and other chemicals by the low concentration of them in the plasma. It is not perfect. Next to the natural organs, with their constant monitoring of levels of necessary nutrients, toxins, etc., this is an inefficient system. But, it can keep a patient healthy and with a reasonable quality of life while on a list for a liver transplant.

What about the dream of an artificial liver that goes into the body to replace the old one and settles in and does its job for years? It may happen some day. Liver cells can regenerate. They do not do well in cell culture, but we may find new techniques to overcome that. Some day, we may be able to vascularize a structure in the same elegant manner as the liver. If the vessels and ducts are not bringing sufficient blood, or taking away sufficient waste, no cell replacement will work. Each hepatocyte has its own network so that it can take in all of the things mentioned and take away all of the things mentioned and more. They do not specialize, so they must all be in contact with vessels and ducts.

Endnote

As the money becomes scarcer, people live longer with more illnesses and insurance companies bring in record profits, some tough decisions lie ahead about even pursuing these goals. Can we afford to keep the rich alive longer and longer, but refuse to provide the most basic medical care to the rest of us? We currently have the highest child mortality rate in the developed world. It is a brave new world, but how can all of us enjoy its fruits?

Activities

One of my overreaching activities will be building a liver quilt or mobile. I will print out paper hexagons and the students will color and cut them out. Art activities are part of my curriculum because of the creativity aspect of relaxation. Learning techniques to deal with stress is an extremely important part of my health

curriculum. I try to make sure they have opportunities to draw, write songs and sing, write and recite poems, make up skits and act throughout the year. The hexagons will represent the hexagonal arrangement of the functional units of the liver. Each student will get several hexagons and build a contiguous surface with them. I am thinking they can put them on cardboard and make a flat presentation of the model or make a mobile with the hexagons by the end. We will start with how they fit together. Then we can add cut pieces of straws at the corners and in the middle to represent the central venule, hepatic arteriole, bile duct, and portal venule. I will push them to color the deoxygenated blood some other color than blue, since they are convinced that veins carry blue blood. I would like them to work on what comes into the hepatocyte and what goes out of it in some physical way, whether writing or making up symbols with a key to what the symbols mean. Over the course of the unit, about two weeks, we will pull them out and work on them.

For an introduction to ethics of transplants, I want to do a Socratic seminar on who should donate organs. I would like to explore the possible abuses that can take place in pushing people to donate organs. I would like them to read Nancy Farmer's book, *The House of the Scorpion*, about a boy who is a clone grown to provide replacement organs for the rich head of the household. I am not sure I can get enough copies, but it would definitely enrich the discussion. This book takes ideas presented in other books about illegal harvesting organs to the limit: human clones are treated as pieces of merchandise to be slaughtered at need. I would also like to bring up experiments that have been done on humans, whether prisoners or people considered sub human by the people in power. We can also discuss books and movies they may know, like "Coma", a thriller about doctors putting people into comas to keep their organs alive to sell. There have also been many stories on criminal groups buying organs to sell in exchange for protection of illegal immigrants.

The second Socratic seminar I would like to do is the ethics of who should receive organs. There are guidelines for doctors to interpret that are specific about who should have priority for a transplant. They attempt to be fair and not subject to the doctor's personal biases. Because there are so many more people who need a transplant than there are available organs, this is a life and death situation and is the type of decision medical providers must make every day. One thing we could take into consideration for our imaginary recipient list is how valuable a contribution the person makes to society. Physicians have tried to get away from that, since it is such an individual judgment, but there are many people who feel that prisoners should not get extreme medical benefits such as this over more productive members of society. There is also the question of people who have destroyed their own livers through their risky behavior. Do they deserve the same consideration as someone who had a genetic illness and did not engage in risky behavior? Of course, then there is the argument that those with defective genes should not be allowed to pass them on to the next generation. What about religion? Above all, there is the money aspect. Who can afford a transplant? Many insurance companies will not pay. Sometimes the state pays. Can we as a public afford that? I can see the possibility of a very rich discussion.

I will assign each student to a group of four and ask them to prepare a power point about one specific drug and include in that:

Why might people abuse that drug?

Is it dangerous?

Does it have a medical use?

Is it addictive?

What are the effects on your body?

Which organs does the drug target?

I can assign a variety of drugs; aspirin, ecstasy, oxycodone, methamphetamine, ritaline, opium, marijuana, and nicotine.

We will also do a short storybook about the liver. I am considering calling it Billie Bile. Each student will be responsible for their own and will be required to include many of the facts they have learned, but using as much creativity as they would like.

We will first brainstorm what criteria students think are used for transplant. Then I will explain the criteria as explained by Dr. Stephen Latham, a prominent bioethicist. I will put the students into groups of four. They will be given instructions that they are to persuade the class that their assigned patient should be first on the list for a transplant. I will assign each group an imaginary person with positive and negative characteristics. Each will be in need of a liver transplant. Each will have a different indicator for a transplant. I will ask each group to write a short essay on why their patient deserves the first liver. Then, I will ask them to act out the discussion among the doctor, the patient and the person who is going to list the priority of each transplant.

I also want them to create a Billy Rubin book. They must focus on transplants. I want them to design their book as an explanation of transplant to a small child. They will be required to do pictures or cartoons, words to explain and some sort of simplified information on how they pick a donor and how they pick a recipient.

After a brief lecture on new artificial organ techniques, I want the students to think about what needs to be included in an artificial organ. We won't spend a lot of time, but I would like this issue to be brought up for some discussion.

Detailed lesson plans

I am planning to use approximately eight lessons, including watching Sicko, a movie I have been showing and discussing, which is about the state of health care in the United States. Eight days for us is approximately three and a half weeks. We are on block scheduling. We alternate two or three classes of one hundred minutes each week.

The first day, we will begin with me showing them my plastic liver, which looks realistic and bloody. Then we will do a brainstorm, writing everything they know about the liver. I may need to prompt them. We will discuss why liver would be an important topic for health. Hopefully, it will be known to some of them that the liver is important in alcohol detoxification, at least. I will explain where the unit is going and what projects they will be expected to complete. I will explain and diagram the cellular structure and circulation of the liver. We will start our hexagon project.

The second day, we will try to brainstorm liver function, which will probably end up as a short lecture by me. I want them to understand how important it is. I will assign the power point presentation on the effects of various drugs, as detailed above. We will go to the computer lab to work on it.

The third day, we will start with a review of structure and function. Then we will move onto our power points. We will move on to a discussion on how the research is going, making sure they are using valid sites, asking what help they need. After this, we will return to the computer lab.

Day four, I will start with a brief lecture and hopefully discussion on organ transplantation. We will start our power point presentations. If they finish early, we will go back to work on our hexagons.

Day five, we will start our Billie Bile storybook. I want to spend at least forty-five minutes on our first Socratic seminar as well. The essential question we will address is "Who should pay for organs and for transplants?"

The sixth day we will again work on the storybook. We will also do our second Socratic seminar, with the essential question, "Who should be first and last on a donor recipient list?" I may do a round robin with large sheets of paper for each student to write their opinions on and then for their classmates to respond silently if two days of Socratic seminar seems too much for the freshmen in the class.

On day seven, we will finish the storybooks, and then share them with the class. I will share with them some of the things I learned about new technology for artificial organs. I will introduce the movie "Sicko". I generally do a disclaimer on Michael Moore and the fact that the documentary we are about to watch shows one man's opinions. He does base those opinions on well-researched facts, however. I have double-checked some of his statistics on the World Health Organization web site. I will give them questions to answer as we watch.

On the eighth day, we will finish "Sicko". We will either do a small group discussion on it or possibly a round robin. I want them to answer several questions.

Who should pay for medical care?

Should we have a single payer system? Are health insurance companies necessary?

Should we spend more on research or on preventative care?

What would you need in an artificial liver?

How are the ethical issues about artificial organs different from the issues involved in transplanted organs?

We will finish with final thoughts and a whip (where each participant makes a brief statement on what they learned or what interests them). I have another movie I would like to show if I have time, called "D-Tour". It is a documentary about a young man on dialysis who does a tour with a rock band. It talks about the difficulties of living a normal life and brings up many of the challenges of transplantation when a living donor offers him a kidney.

Bibliography

Boron, Walter F., and Emile L. Boulpaep. *Medical physiology: a cellular and molecular approach*. Updated ed. Philadelphia, Pa.: Elsevier Saunders, 2005.

This book was helpful because of its detailed information about the liver. I could find details about all of the interactions of liver cells

with their environment and their contributions to our hemostasis.

Kapit, Wynn, Robert I. Macey, and Esmail Meisami. *The physiology coloring book* . 2nd ed. San Francisco: Addison Wesley Longman, 2000.

This was very helpful as an introduction to the general organization of the body, its systems and organs.

Latham, Stephen. This bioethicist from The American Society for Bioethics and Humanity gave me great insight into the machinery behind the transplant business.

Lee, William M., and Roger Williams. *Acute liver failure* . Cambridge: Cambridge University Press, 1997.

This book gave me in depth information on acute liver failure due to viral hepatitis and various drugs.

Marieb, Elaine Nicpon. *Study guide, Human anatomy & physiology, fifth edition* . 5th ed. San Francisco: Benjamin Cummings, 2001.

This book was extremely helpful with general background information about the liver and its normal functioning.

Palmer, Melissa. *Dr. Melissa Palmer's guide to hepatitis & liver disease* . New York, NY: Avery, 2000.

This book contained an overview of the effects of viral hepatitis on the liver.

Reddy, K. Rajender, and Thomas Faust. *The clinician's guide to liver disease* . Thorofare, NJ: SLACK Inc., 2006.

This book gave me information on the effects of viral hepatitis and drug intoxication on the liver.

Shannon, Joyce Brennfleck. *Liver disorders sourcebook: basic consumer health information about the liver and how it works; liver diseases, including cancer, cirrhosis, hepatitis, and toxic and drug related diseases; tips for maintaining a healthy liver; laboratory tests; radiology*. Detroit, Mich.: Omnigraphics, 2000.

This was a useful book on the liver disorders I was writing about and more insight into the normal liver functions, as well.

Saltzman, W. Mark. This Yale professor gave me great insights into the working of the human body in general, the liver in particular and modern medical advances in treatments of liver disorders, especially strides made in artificial livers.*Chicago formatting by BibMe.org*

Appendix

California Department of Education Health Education Content Standards, March 2008

1.1.ADescribe the health benefits of abstaining from or discontinuing use of alcohol, tobacco, and other drugs. We will address this when students do power points on the effects of drugs on the liver.

1.7.AAnalyze the consequences of binge drinking and its relationship to cancer; to liver, pancreatic, and cardiovascular diseases; and to a variety of gastrointestinal problems, neurological disorders, and reproductive system disorders. We will look at the effects of alcohol use on liver.

2.1.AEvaluate strategies for managing the impact of internal and external influences on alcohol, tobacco, and other drug use. We will look at impacts of the use of various drugs on the liver.

3.1.AAccess information, products, and services related to the use of alcohol, tobacco, and other drugs. We will look closely at information about the use of these drugs.

3.2.AEvaluate prevention, intervention, and treatment resources and programs concerning alcohol, tobacco, and other drugs. We will look at prevention through knowledge about the effects of drugs on the body.

6.1.APredict how a drug-free lifestyle will support the achievement of short- and long-term goals. This will be implied in the functions of a normal liver.

8.2.APresent a persuasive solution to the problem of alcohol, tobacco, and other drug use among youths. Hopefully, the physical effects of drugs on their organs will be persuasive.

1.3.PIdentify symptoms that should prompt individuals to seek health care. Symptoms of liver disease will be studied.

1.4.PIdentify types of pathogens that cause disease. We will focus on HBV and HCV, both contagious pathogens.

1.5.PInvestigate the causes and symptoms of communicable and non-communicable diseases. We will be looking closely at many liver diseases.

1.10.PExplain how public health policies and government regulations influence health promotion and disease prevention. We will discuss at length the problems of the medical system in the USA and how policy makers affect the cost and denial rate of medical care.

2.1.PDiscuss influences that affect positive health practices. We will cover this throughout the unit, discussing effects of unprotected sex (HBV), piercing and tattoos (HCV), and various drugs that affect the liver.

2.6.PEvaluate the benefits of informed health choices. Covered throughout this unit in the effects on the body of poor health choices.

5.1.PApply a decision-making process to a personal health issue or problem. We will discuss negative consequences of many things common among teens.

5.2.PExplain how decisions regarding health behaviors have consequences for oneself and others. The money involved in transplants is a major consequence for preventable disease.

5.3.PApply a decision-making process to a community or environmental health issue. We will discuss the ethics of transplant.

5.4.PAnalyze how using alcohol, tobacco, and other drugs influences health and other behaviors. We will study the direct effects on health.

5.5.PAnalyze the possible consequences of risky hygienic and health behaviors and fads (e.g., tattooing, body piercing, sun exposure, and sound volume). Tattooing and body piercing are part of our HCV study.

6.1.PDevelop a plan of preventive health management. We will focus on drugs and risky behavior, but also discuss what responsibility we have for our own behavior as it relates to transplant eligibility.