

July 2005 Issue | Clinician/Researcher of the Month Burton M. Berkson, MD, MS, PhD

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Welcome to *Functional Medicine Update* for July 2005. In the *Wall Street Journal* in 1991, there was an amazing report that still strikes me as being of significance today. It was a report about a gentleman who lived just outside of Dallas, Texas. He was a successful petrochemical engineer who, like all of his neighbors, cherished his home, his garden, and his lawn. One Saturday afternoon, he was manicuring, mowing, and pruning his lawn, using the appropriate fertilizer to make his little plot in the world aesthetically attractive. The following day, he wasn't feeling very well. He had a headache and general malaise, and it didn't get better. On Monday morning, he felt worse and his condition deteriorated throughout the rest of the week. Over the course of the next month, he became seriously ill and he went to his physician. He was jaundiced, with elevated liver enzymes, and it appeared that he had some type of idiopathic inflammatory condition of the liver. The condition worsened until it got so bad that he had fulminant liver failure and required a liver transplant.

After six years and 20 doctors, liver biopsies, CAR scans, radioactive brain flow studies, and many months of anguish, it was recognized that his problem must have been a consequence of his exposure to the biocides and weed killers in the fertilizer he had used on his lawn, in combination with regularly taking cimetidine (Tagamet) for his hyperacidity. The combination of cimetidine with its effect on a cytochrome P450 (probably 1A2) enzyme in the liver, and exposure to a biocide requiring detoxification via that P450 pathway for elimination from the body, led to a dangerous and perilous outcome which, in his case, was serious liver dysfunction. This case contributed to the eventual warning on the medication label about the simultaneous use of cimetidine and exposure to environmental toxins.¹

Similarly, acetaminophen was also implicated in a case of serious liver failure, which ended up in court. The origin of this story goes back to a 39-year-old man who was drinking wine every night and taking extra strength acetaminophen. He ended up with a kidney transplant and sued McNeil Consumer Products for not having an appropriate warning on their product. As a result, in 1995, the FDA Advisory Committee recommended that all over-the-counter pain relievers such as acetaminophen carry the alcohol warning: "If you generally consume three or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take this product and other pain relievers." Now, although in fine print, there is a warning label on this medication concerning the use of alcohol simultaneously with acetaminophen. And, although the risk is generally considered to be related to the amount of alcohol, data indicate the way a person handles alcohol is a factor. Therefore, some people may be more susceptible to this effect at lower amounts of alcohol consumption than three drinks per day.²

What am I speaking to here? The focus of this month's FMU will be on the liver, or functional hepatology. Where do these unusual idiopathic, liver-related problems come from? Why is chronic liver disease now associated with 3 billion dollars of healthcare expenditures annually for conditions of unknown origin? What is the origin of chronic liver problems? Why are we seeing more hepatitis C, biliary cirrhosis, cholangitis, and other types of problems with no specific focus of origin or etiology? It is those questions I want to focus on in this month's FMU—a first in our 23-year history—looking specifically at the liver from a functional hepatology perspective.

In order to do this, we need to mention Dr. Sheila Sherlock, one of the primary investigators who helped us understand the metabolic, immune, and endocrine functions of the liver. Dr. Sherlock, who recently passed away, would certainly be considered one of the great pioneers in our more modern understanding of liver function.

Liver Function

When we talk about the liver, we are talking about a variety of truly remarkable functions. In fact, as we go through the list, we wonder how we could even speculate on living a normal, healthy life without high-level liver function. The liver is a metabolic organ; it is an immune organ; it is an endocrine organ. As a consequence, it controls much of the switching of nutrients and signaling molecules, the relationship of immune defense and elimination of potential endogenous and exogenous toxins, and the handling of metabolic recycling of nutrients (glucose, fatty acids, and amino acids). It is the organ of choice the body uses to detoxify the toxic, nitrogen-containing molecules that we call amino acids. When I say toxic, I say it somewhat tongue in cheek, because amino acids are certainly necessary in the diet for the support of proper protein nutrition. But the nitrogen atoms in protein molecules, as part of the amino acid structure, are uniquely difficult to eliminate from the body, and require a specialized detoxification pathway found almost exclusively in the liver, called the urea cycle.

The Urea Cycle

Humans get rid of nitrogen through a complex, neutral, non-pH-modifying, nitrogen-containing excretory product called urea. This is in contrast to other animals that can eliminate nitrogen by way of ammonia release, and who have a whole different physiological system for handling the pH effects that the ammonium ion has on both extracellular fluids and tissues. In the human, however, the excretory route for ammonia is the neutral molecule, urea, which is two ammonias stuck to a carbon monoxide molecule to make it a urea molecule—a neutral pH and electrolyte-neutral species. The liver engages in this very unique process for detoxification and elimination of extra nitrogen that comes, in part, from excess dietary protein.

Albumin Synthesis

The liver also plays a very important role in synthesizing specific plasma proteins, not the least of which is the major plasma protein albumin, upon which are bound and transported many substances that are delivered at adjacent and distant sites where they are taken up by tissues. Albumin synthesis is a very important part of liver function.

Apolipoprotein Synthesis

What about apolipoproteins, the protein constituents necessary for transportation of the fat-soluble substances like lipids, which are water insoluble and, therefore, insoluble in plasma? They need to be transported in a conducted-tour mechanism around the body on a water-solubilizing agent, which is an

apolipoprotein synthesized by the liver.

Emulsification of Fats

What about the emulsification of fats? Fats in and of themselves cannot be well absorbed into the body because they are fat soluble, and the body is principally made up of water. They need to be emulsified with detergents in the digestive tract in order to get them into a form, a so-called micelle, so they can ultimately be taken up as small particles into cells and used as metabolic fuel. This occurs by way of emulsification with bile. Bile is composed of three constituents—cholesterol and its esters, bile salts derived from cholesterol by way of hepatic metabolism, and lecithin as an emulsifying phospholipid, which is also synthesized by the liver.

Fat, Protein, and Carbohydrate Metabolism and Cholesterol Synthesis

The liver plays a very important role in fat, protein, and carbohydrate metabolism. It is also the major organ for synthesis of cholesterol. An important physiological regulatory step occurs when 3-hydroxy-3-methylglutaryl CoA is converted to mevalonic acid. The enzyme responsible—HMG-CoA can be inhibited by a variety of physiological factors, probably the most important of which is the intracellular level of cholesterol. HMG-CoA reductase is the enzyme that statins presumably block to prevent cholesterol synthesis in the liver.

This is only a partial list of liver functions. To fully understand the liver's importance and functionality in human physiology would require a lifetime of work. It is an extraordinarily dynamic organ that can also regenerate itself. It can hypertrophy; it can be smaller in size when it is not stressed for its work. It can be regenerated when it is injured. There can be an extraordinary number of messenger molecules that influence liver function, including things like erythropoietin and other types of neurosensory and neurologic hormonal substances.

Kupffer Cells, MALT and GALT

The liver is a very important, dynamic tissue that is engaged in real-time functional change in response to the environment. Its unique function is, in part, encoded in the genetics of the individual, and therefore another demonstration of the gene/environment connection. It is composed of a variety of different cell types. One cell type that occupies about 10 percent of the liver mass is called the Kupffer cell, which is an embedded white cell having to do with the liver's immunological function. The Kupffer cell takes its messages from the information it receives by way of the hepatportal blood that passes by the gastrointestinal (GI) mucosal system. The GI mucosal system is where most of the body's immune system is clustered. About 60 percent of the cells and about 75 percent of the antibodies are manufactured and are present in the mucosal-associated lymphoid tissue (MALT) and the GI-associated lymphoid tissue (GALT). These activated tissues in the gut send signals by way of intercellular communication and signal transduction. The Kupffer cells in the liver pick up messages, such as those from interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-a), and interferon gamma. Those relay batons are taken up and transmitted by the liver cells, which secrete autocrine and paracrine types of substances and inflammatory mediators that can alter immunological function systemically as well as regionally. The liver might also be considered an immune organ with an inflammatory capability or personality.

Oxidative Stress in the Liver

Dr. Helmut Sies, father of the term "oxidative stress," first studied many of these oxidative reactions in liver tissue. The liver is actively engaged in what are called oxygenase enzyme activities, the combination

of oxygen with various molecules to produce hydroxylated or oxygenated outcome derivatives. Those enzymes can influence localized tissue by releasing oxidants that can damage adjacent cellular function and, in the case of redox control, can uncouple mitochondria in the liver, thereby releasing electrons to become oxidants and further serve as pathogenic agents to induce hepatotoxicity, or oxidative stress in the liver. The reduction/oxidation association with cellular physiology has been, to a great extent, studied in liver tissue because it is such an active oxidative organ involved with the oxidative/reductive chemistry of life through mitochondrial function and the combination of oxygen with enzyme function to produce oxygenated derivatives.

Hemoglobin Metabolism, Porphyrins, Anabolism, and Catabolism

Porphyrin and hemoglobin metabolism also takes place in the liver. Bilirubin is an indicator of hepatobiliary dysfunction that is, in part, a breakdown product from hemoglobin through porphyrin metabolism. It is also associated with liver function and has multiple responsibilities for building things up (anabolism), such as proteins, triglycerides, phospholipids, and glycogen, and breaking things down (catabolism), such as detoxification and metabolic catabolic reactions that occur in the liver to reduce high-energy food molecules—fats, protein, and carbohydrates—into small molecules like carbon dioxide and water, plus energy. That is catabolism—converting big molecules to small ones. The liver is both an anabolic organ and a catabolic organ and it carries out both of those functions simultaneously. It is not as if we can make a general statement to the effect that the body is in anabolism or the body is in catabolism. It is undergoing both of those processes, and the liver is a dynamic organ in which those things are engaged in real time all the time—breaking things down and building things up.

Environmental Changes and Liver Function

There is pressure on liver function as the environment changes and various substances to which the liver is exposed are altered. Obviously, one of those substances is drugs, or pharmaceuticals. Others are alcohol, and the type of nutrition that we are consuming. The liver also has to deal with byproducts of gut bacterial metabolism—enteric bacteria—that release their own byproducts into the portal blood, arrive at the liver, and must be metabolized.

Liver Function and Increased Central Body Fat

Certainly, in the 21st century, we also need to consider the liver-related stress that accompanies increased central body fat accumulation. If a person has a lot of visceral adipose tissue, that fat has access for secretion into the portal blood that goes directly to the liver various adipokines, or reactive inflammatory molecules that come directly from fat cells deposited in the visceral adipose tissue.

There are a lot of things going on in the liver simultaneously and it may be the interrelationship between liver functional reserve and the liver stress factor that ultimately starts tipping the balance toward the increasing prevalence we see of these chronic liver diseases of unknown origin.

I want to go through a few of the more sensible things that come out of this discussion from a clinical perspective. First, what feeds the liver? How does the liver get its nutrients? It can only get its nutrients from the nourishment that is provided to it from food. Food is processed through the digestive system and ultimately delivers the broken-down components as small molecules that get absorbed in the portal blood and ultimately transferred to the liver. In the simplest terms, we think of glucose and other small sugars coming from carbohydrate, free fatty acids or triglycerides coming from fat, and amino acids or very small peptides coming from protein, but this is only a part of the story. There are many other molecules

that also come from the diet.

Hepatic Encephalopathy

There are other molecules that come by way of absorption from the GI tract that can induce alterations in liver function. They include things we associate with hepatic encephalopathy. We really should call this GI hepatoencephalopathy because the molecules of origin were derived from the gut through bacterial fermentation; when they arrived at the liver they couldn't be adequately scrubbed from the blood, and thus they were delivered into plasma to the brain, where they can produce chemical mimetic effects on brain biochemical behavioral influence. There is an interrelationship between molecules produced in the gut and those that serve as putative neurotransmitters or neuromodulators in the brain, as connected through the liver into the blood.

Treatment for Hepatic Encephalopathy

When we talk about a patient who has a psychosis or hallucinations of hepatic encephalopathy, it is an interesting case in point. The traditional treatment of choice would be to put them on something like lactulose, which causes diarrhea and purges the GI tract, while trying to feed them intravenously and take a load off their gut. Another approach that has been used is to put these patients on a low-protein diet and give them an elemental, or lower-allergy diet, which also lowers the load of strange metabolites on their brain and reduces some of the central nervous system effects. Obviously, the use of a low-protein diet is to lower the load of nitrogenous waste products from bacterial putrefaction. The bacterial putrefaction of protein can produce funny nitrogenous materials, such as cadaverine and putresine. The names alone suggest their origin. These are biogenic amine compounds that can modify function. They are middle molecular-weight molecules and, in cases of compromised liver function, a person might end up with a problem related to the ability to purge them, after which they get delivered into the blood where they can have an effect on tissues. That is one example of something that comes directly from the gut into the liver that has to be processed.

Quick-Release versus Time-Release Carbohydrates

In simple carbohydrate diets, quick-release carbohydrates end up as simple sugars, such as a pure glucose, during first pass into the liver. That can lead to hyperlipidemia and hypertriglyceridemia associated with sugar intolerance. The liver is a sentinel organ for absorbing the metabolic insult from rapidly metabolized and absorbed carbohydrates in the form of simple sugars. That also tells us something about the difference between a complex carbohydrate, in which simple sugars are time-released, as compared to the quick-release form, such as those found in a candy bar. These time-released carbohydrates may contain the same number of grams of glucose, but the kinetics of glucose absorption and the effect it has on liver fat synthesis are vastly different — glucose that is time-released over hours, such as that from unrefined complex starch (versus a highly purified simple carbohydrate mono- or disaccharide), can influence the endocrine system in a different way.

Formation of Bile Salts in the Liver

The liver is a metabolic organ that takes information from food. The liver also synthesizes bile and it does so through the manufacture of bile acids, which are hydroxylated derivatives of cholesterol; 7-dehydro-cholesterol is a product of the first rate-limiting step in the formation of bile salts. This dehydrogenation reaction, the synthesis process for bile salts in the liver, can be activated by such things as vitamin C or magnesium. Therefore, nutritional status plays a role in improving bile acid synthesis and encouraging proper composition of bile where the emulsifying fat-solubilizing components of bile are the bile salts

that come from cholesterol. It is interesting that when a person has an elevated blood cholesterol level, they often have a low bile salt level because of a block in the dam, so to speak, that prevents the cholesterol from flowing downstream. The way the body gets rid of cholesterol is by conversion to bile and excretion in feces. If there is a blockage in the dam, there is not as much conversion of bile. There are light-colored stools, fat malabsorption, cholecystitis, and increased risk to coronary heart disease (CHD) because of hypercholesterolemia. Does that mean that high cholesterol and bile-related problems such as cholestatic disease are interrelated? The answer is yes. Heart disease and gall bladder disease are interrelated. By improving bile acid synthesis, cholesterol is lowered and two things are accomplished at the same time. Increasing functionality of fat digestion lowers the risk to CHD and also lowers the risk to gall bladder disease. When we begin to look at liver function as a web, we see that there is a lot of interconnection between the individual and his or her environment, genotype, and outcome, as it relates to the multiple functions of the liver.

Detoxification

One of the most interesting emerging themes in medicine is the development of what is called pharmacogenomics, or pharmacogenetics—the genetic tendency toward fast, slow, or normal metabolism of specific molecules due to genetic differences in the detoxification phase 1 and phase 2 systems. People with recurrent adverse effects from various medications may have unique polymorphisms of the detoxification enzyme systems that make them "yellow canaries," whereas other individuals can tolerate the same dose on a body surface area basis. I am always intrigued when I think about this. Of all the human functions that have been studied, the one that appears to have the greatest difference among apparently healthy people is the first-pass detoxification of various substances. There have been data published showing that the difference between one presumably healthy person and another in how they detoxify a substance can vary by a factor of three orders of magnitude, or a thousand-fold. I know of no other physiological function in normal individuals that can vary so widely as that of the pharmacogenomic control of detoxification. This explains the "yellow canary" effect we often see in the population with environmentally sensitive individuals. We wonder why they seem so exquisitely sensitive at such low exposure rates, and often it is implied that they may be suffering from a psychogenic illness. It may all be in their minds, but perhaps it is in their minds biochemically as a consequence of toxicity related to the fact that they are slow metabolizers of a particular substance. Or, they may be on the other side. They may be rapid metabolizers who have much higher turnover than slow metabolizers for a specific substance. In that case, their genetics are such that for that particular substance, the blood level never gets into a therapeutic range and that person does not have a good response with a specific drug because they eliminate it so rapidly.

Grapefruit Juice and Liver Enzymes

This discovery has been exploited to some extent. In fact, Sheila Sherlock was involved with some of these discoveries because it was found that the rate of first-pass detoxification for some substances could be slowed down by administering a material that could block or retard the activity of that cytochrome P450 enzyme. In the case of the cytochrome P450 phase 1 enzymes involved with the metabolism of birth control pills and the very expensive organ-rejection inhibitor, cyclosporin, which costs thousands of dollars per administration, the substance called naringenin appears to retard the rate of detoxification in excretion, resulting in blood levels that are kept higher for a longer time. This is a flavonoid found in grapefruit, and that is why you will now find people talking about being cautious about drinking grapefruit juice when on medication because it can alter the rate of detoxification, or the effectiveness of that medication. It lowers the activity of specific cytochromes, inhibiting to some extent the activity of

those enzymes keeps the molecule of interest in the body longer, resulting in improved activity of that drug. This has been used in the field of transplant surgery. In fact, I first saw this described in the journal *Transplant* 10 years ago. Surgeons were showing that if you have a patient on cyclosporin, administering 300 cc of grapefruit juice a day can greatly increase the efficacy of that drug because the body retains it longer and it does not get detoxified right away.³

There is another part to that story. That is, by blocking that enzyme, it could not detoxify something that you needed to get rid of through a specific pathway, like the enzyme cytochrome P450 1A1. We have certain bifunctional inducers in our diet that modulate both phase 1 and phase 2 detoxification activity, and they can be used for normalizing or personalizing the diet intake for a patient with specific hepatic detoxification abnormalities. For instance, cruciferous vegetables have an effect on detoxification by upregulating phase 2 quinone reductase and glutathione S-transferase, resulting in better phase 2 detoxification to balance out the altered phase 1 detoxification, and trying to keep the system in balance to eliminate molecules in a safe way by minimizing the formation of intermediary toxic molecules, the so-called biotransformed intermediates.

The diet can be used selectively to personalize the needs of the individual for improved detoxification function—another rapidly emerging and interesting field in medicine that falls under the banner of pharmacogenomics. It is interesting as it relates to prescribing patterns of various prescription drugs. As science has started to develop an understanding of these inducible phase 1 and phase 2 enzyme systems and how they are influenced by various drugs, there is now a test that can screen very rapidly for the pharmacogenomics of detoxification enzymes that identifies the toxic genome relationships and the ability of the genome to regulate the enzymes involved with detoxification. It is now being suggested that patients should be screened by these tests before putting them on certain drugs, so their potential for adverse effects is known. These tests determine whether a patient is a slow or fast metabolizer. Patients should be screened for potential adverse response to the drug Imuran based upon an MTPT assessment of their genotype. This is the methylthiopurine transferase enzyme involved with the detoxification of that drug. Slow metabolizers should not be put on that drug for fear of adverse response, or the dose should be adjusted appropriately.

Similarly, recall the story I described in the beginning of this issue of FMU, which describes what happens when taking cimetidine and experiencing concurrent exposure to toxic biocides. There is an increased risk for adverse side effects because the cimetidine blocks the detoxification of various biocides and therefore makes a person more susceptible to xenobiotic toxicity. A person should be off medications that could adversely affect detoxification if they are going to be exposed to these xenobiotics.

Alcohol and Liver Detoxification

That same theme applies to alcohol consumption. Charles Lieber, whose name I have brought up in previous issues of FMU over the years, is a highly regarded primary investigator in the area of alcoholism and understanding alcohol's mode of action on inducing liver dysfunction. He has talked at length about the alcohol addiction problem, but more interestingly, he has discussed the adverse influence of alcohol on detoxification pathways. One of the things he has shown, and I believe he was the first to demonstrate this in primates, is that when a considerable amount of alcohol is consumed, it goes beyond normal metabolism in the liver (through alcohol dehydrogenase), to activate a second detoxifying system—the cytochrome P450 system (cytochrome P450 2E1). When this enzyme is upregulated by excessive alcohol consumption, it produces a very high level of oxidized intermediates in the liver which have to be

detoxified by phase 2 conjugation with glutathione. Therefore, the depletion of glutathione can occur very rapidly in a person who is abusing alcohol, particularly if he or she is not eating an appropriate diet. That results in the accumulation of these very toxic materials because they have nowhere to go. They basically cannot be detoxified by glutathione conjugation. In these cases, patients end up with a hepatic-induced neurological illness called delirium tremens (DTs). The treatment of choice for these patients in the ER is to administer the compound N-acetylcysteine, or Mucomist by intubation or gastric tube, which seeks to trap the free radical oxidants generated in the liver by upregulation of CYP 1E2, in an attempt to block oxidative injury to the liver.

What Dr. Leiber points out is that the variation among individuals and how quickly they can develop liver injury due to this process is quite dramatic, based upon their genetic uniqueness related to glutathione S-transferase activity and oxidative chemistry. This is discussed in a review paper in *Critical Review of Clinical Laboratory Science*.⁴ It shows that inhibiting liver injury (cirrhosis) in an alcoholic, can be accomplished by blocking the oxidative damage due to depletion of glutathione. Glutathione, N-acetylcysteine, and various antioxidants can be used to try to promote proper function.

This is another example of how nutrition interfaces with liver function, providing protection against the environment. We certainly consider the liver as an important barrier organ for defending and protecting us against toxic endogenous and exogenous substances.

The Liver and Its Role in Transamination and Deamination

That takes us into the role of the liver in transamination, deamination and rearrangement of protein through the process of the so-called transaminase enzymes, which are activated by coenzymes such as pyridoxal phosphate. Vitamin B6 becomes a very important part of the liver protein metabolic sufficiency argument. Just as with patients on high carbohydrate diets who need high doses of vitamin B1 to properly metabolize carbohydrate, individuals on a high protein diet need adequate vitamin B6 in order to manage their amino acids.

There is also cholesterol biosynthesis. Cholesterol is manufactured in the liver and is transported out of the liver into the plasma by apolipoproteins manufactured in the liver. Those are genetically controlled, as well. This is a feedback process through the LDL receptor, which Brown and Goldstein have told us about.⁵

The 4R Program™

That takes us back to the control of liver function upstream which is, in part, related to what is going on in the GI tract. What about the use of the 4R Program (remove, replace, reinoculate and repair), for improving GI and hepatic function? There is a marvelous paper discussing the use of pre- and probiotics for the management of hepatic dysfunction in hepatic encephalopathies, and it demonstrates a role for reinoculating the gut and establishing proper gut floral integrity and gut immune function to support hepatic function and brain chemistry. This article appeared in *Medical Hypotheses*.⁶

As we begin to explore this in greater detail, we see that the liver has many remarkable effects, one of which I have not discussed in detail, that of immune function, which includes the Kupffer cell function of the liver and how it responds to immunological activators. Just as with all other white cells of the cell-mediated innate immune system, the particular activity of the Kupffer cells is modified by exposure from the portal blood to various types of proinflammatory mediators—IL-1, IL-2, and TNFα;—which are

products that are often released by the systemic immune system or GI-associated immune cells. When improving liver function in people with various types of inflammatory liver diseases, including cholangitis, biliary cirrhosis, and hepatitis, one needs to be concerned about viral titers, as well as lowering the load of proinflammatory materials—food allergens, antigens, xenobiotics, and heavy metals—and then trying to improve liver antioxidant defense, redox cycling, and detoxification abilities.

The general theme that emerges is that perhaps many chronic diseases of fatigue, muscle pain, sleep disturbances, restlessness, and all components of a low-energy syndrome are, in fact, related to slight overburden of the liver's detoxifying and regenerative abilities. Although liver function tests may be "within normal range," the functional ability of the liver is to process these materials and to eliminate them effectively, but not deliver secondary metabolites into plasma that could alter cell membrane receptor activity at distant sites, producing suboptimal function, as if the body was "under alarm." That brings us back to what kind of diet, life style, and therapeutic programs would help to enhance or normalize these detoxifying and cellular regulatory capabilities. That leads to one of the fundamental tools in functional medicine that goes beyond the 4R Program for restoration of GI immune function.

There is a concomitant program called metabolic detoxification using an elemental diet, one that is very rich in the nutrients necessary for support of proper phase 1 and phase 2 detoxification that gives rise to an extraordinary positive potential outcome in patients with chronic liver and gut-related dysfunctions that are seen as symptoms of unknown origin and which may be related to dysfunction of the gut and liver interaction.

That leads us to our COM interview that will take this discussion to a whole different level and should add some clinical tools to your tool kit.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
Burton M. Berkson, MD, MS, PhD
1155 Commerce Drive
Las Cruces, New Mexico
88011 bberkson@nmsu.edu

JB: It's time for our Clinician/Researcher of the month, and we are very fortunate to have Dr. Burton Berkson as our guest. We interviewed Dr. Berkson on FMU in June 1996 and have been following his work related to the modulation of hepatotoxicity and hepatic oxidative stress. I want to mention one anecdote before we get into our discussion.

I often receive feedback from people about what they've learned from the material in FMU. I received more feedback from my previous discussion with Dr. Berkson on FMU than from any other in the last 23 years. One gentleman told me that Dr. Berkson's therapy represented one of the most remarkable tools he has used in his medical practice. He had two patients with progressive liver failure who were candidates for liver transplants. Introducing what he had learned from Dr. Berkson some years ago led to recovery in both of those patients. Neither of them needed liver transplants and very good liver function was resumed in both cases. Those are miracles, by any stretch of the imagination. But the difference between miracles in reproducible medicine that become the standard of practice is an understanding of why they are miracles. That's what Dr. Berkson has helped us to understand.

I want to briefly cover some of Dr. Berkson's background. His training included a variety of very high-level science experiences, including a PhD from the University of Illinois, followed by work in clinical mycology as a visiting scientist at the Max Planck Institute. He was an assistant professor at Rutgers University. He moved from emergency medicine to the establishment of his own integrative medicine center in Las Cruces, New Mexico. That is a wide swath of experience and accomplishment. It's with great pleasure, Burt, that we welcome you back to FMU.

BB: It's a pleasure, Jeff.

JB: For those who were not fortunate enough to have heard our first interview, let's revisit your experience with amanita mushroom poisoning and how that led you to some insights and "ahas." This would be a good place to start before we move on with the discussion.

Treatment of Mushroom Poisoning with Alpha Lipoic Acid

BB: Back in the late 1970s, I was an internal medicine resident in Cleveland, Ohio at one of the university hospitals, and I was asked to take care of two people who had hepatotoxic mushroom poisoning. I was told that there was really no hope for them. Their livers were shot, it was impossible to get liver transplants, and I was told that they would surely die. PhDs are always looking for new things, so I called Washington, DC and spoke to Dr. Fred Bartter, who was then chief of endocrinology at the National Institutes of Health. Dr. Bartter told me he was using alpha lipoic acid as a treatment for diabetic neuropathy and that his patients appeared to regenerate organ tissue after receiving it. He sent it to me, I gave it to my two patients with mushroom poisoning, and it regenerated their livers.⁷ It was remarkable.

JB: Did you find that the liver enzyme levels in these patients came down in a fairly rapid fashion? Did it take weeks, months, or years of therapy? What was the rate of response?

BB: The rate of response was about two weeks. When they came in, their liver enzyme levels were in the thousands. Within two weeks, their liver function was normal.

JB: When I heard you present this information for the first time, I had a sense of incredulity of how something that is so powerful and so useful is not a standard of practice, and not on the lips of every practitioner who is seeing the increasing prevalence of liver-related problems. Why?

BB: Dr. Bartter and I were the principal investigators on lipoic acid for the FDA. We went to most of the pharmaceutical companies, but they had no interest in lipoic acid because it was a drug that had been patented by the Germans and they weren't able to get full exclusivity to it. It seems that in order to get a drug through the FDA, it costs hundreds of millions of dollars. If they manufacture it and don't have full exclusivity, another company can compete with them, and they don't get a return on their money. I think this is one of the major reasons, but there are other reasons, too.

Dr. Bartter and I published two papers on 79 people with severe hepatotoxic poisoning.⁸ They had acute hepatic necrosis. These 79 people had to be declared terminal before Dr. Bartter and I would administer to them at various medical centers across the country. All we did was give them alpha lipoic acid, and it regenerated the livers of 75 out of the 79 patients. Most of them are still alive today and I am in contact

with them.

When we first went around speaking about this at various universities, the first question would often be based on the fact that Dr. Bartter was the chief of endocrinology at NIH, and probably the world expert on diabetes and kidney disease, so people would ask what right he had to treat liver disease? Dr. Bartter would often refer to me because I had discovered that livers could be regenerated easily with lipoic acid, and perhaps other organs, too. That would result in a response to the effect that I was a microbiologist, and if I wanted to work on liver disease, "why didn't I become a board-certified hepatologist?" There is a kind of arrogance in all professions where, if you're in a field somewhat different from the field they're in, they feel you're encroaching on their turf and they just don't like to hear that. I think that's part of the problem. If we had been hepatologists, this probably would have been more readily acceptable to them.

JB: I recall a number of years ago, we interviewed Dr. James Goodwin from the University of Texas School of Medicine. He had written an article that received quite a bit of attention, titled "The Tomato Effect," in which he talked about why things are not discovered and why things lie dormant for a long period of time.⁹ He followed that up with another interesting paper that was published in the Archives of Internal Medicine in 1998, in which he talked about what you're referring to, which he called "the guild."¹⁰ He asked why nutritional therapies had been the least accepted therapies in medicine and why they have such vitriolic, contradictory, and damning literature in some of the traditional medical textbooks. He pointed out that if you look at the language in some of the classic medical books that students learn from, the concepts of nutrition, particularly supplementation with specific micronutrients, are vilified with language that you don't find in any other field, and he asked why. He concluded that when people are speaking about these things, they step out of "the guild." He used Linus Pauling as an example, saying that if you keep within the guild, as you mentioned (the closely held specialties), then everybody feels he or she is part of the club, no one will look bad, and everybody is in a comfort zone. Once you take it to the public, or out of the guild, you become like Galileo. The problem with Galileo, he pointed out, wasn't his heliocentric view of the universe. That was already well known from Kepler. He took his view out of the language of the scholars, which was Latin, into the language of the people, which was basically Italian. When he did that, it really broke the trust of the guild. It sounds like that's analogous to what you're describing with lipoic acid.

BB: I think it is. Also, I remember years ago, I once heard a lecture by a female economist. She said that there are many good ideas, but no good idea really becomes accepted by the general public and the people involved unless there's big money behind it. I don't think any big corporation would be interested in alpha lipoic acid as a drug (that's where the money is), unless they get good exclusivity on it and make a great return on their money. Right now, it appears that would be difficult.

JB: Let's go back and explore what you've learned in terms of dosage and safety concerns. Everything at some dose is toxic, including air and water. We always want to know where the parabolic dose-response curve safety range lies. What dosage have you found useful in these applications?

BB: It depends on the person. LD50 studies were done for intravenous lipoic acid. These studies were done years ago at the White Sands Primate Research Center in Alamogordo, New Mexico. The work was done by Hill and Couch. They found that giving primates 100 mg per kg killed most of them. Intravenously, it would be quite a bit less than 100 mg per kg. They asked me to do the electron microscopy on the livers of the animals that had died. I've yet to publish it, but it's almost ready. It seems

that lipoic acid in very high doses causes the mitochondria to explode. It seems to rev up mitochondrion oxidative respiration and they seem to break apart. The cristae fall apart; the membranes fall apart. When I looked at the necropsy specimens from these animals, there were large necrotic areas in the liver, in the heart, and in the large muscles of the leg. It seems that lipoic acid is a very effective mitochondrial stimulant and, in very high doses, it probably works so quickly and effectively that there's just not enough oxygen or acetyl CoA available, and they just heat and blow up. It was an amazing discovery that we made on this autopsy tissue.

When Dr. Bartter and I started out in the 1970s, we used to give the patients (intravenously at first, with humans), a test dose of 50 to 100 mg of lipoic acid, just to make sure we weren't dealing with any allergies or sensitivities. We'd work up to about 100 mg four times a day IV. As time went on, I found that lipoic acid doesn't only work for acute liver disease, but it's also very effective for chronic liver disease, such as hepatitis C and B, primary biliary cirrhosis, autoimmune hepatitis, and a whole range of things. I went up to anywhere between 100 mg to, in some cases, 600 mg IV for these patients. In addition, they're all on 300 mg orally twice a day.

JB: Can you get the same results without IV administration, or is it very important to deliver directly to the portal blood by IV?

BB: For many of our patients with liver disease, just the oral administration is effective. The people I see with hepatitis are usually folks that have been told there's no hope. They've been through the interferon and ribavirin therapies, or other therapies—Imuran and prednisone for autoimmune hepatitis. Oftentimes, they have full-blown cirrhosis and they come in with portal hypertension, esophageal varices, ascites, and they look like they're about to die. These people have oxidative stress in all the tissues of their bodies. We usually start them on an oral program, but we also give them alpha lipoic acid IV one or twice a day for five to ten days.¹¹

One person came from North Africa with a whole entourage of cooks and bodyguards. He was an important man there. He stayed for three months and seemed to do very well after that period of time. He had been told by someone at one of the big northeastern medical schools that there was no hope; he should just go back to Africa and die. When he left our place, he was doing very well.

JB: You mentioned an interesting sidebar that I want to pick up on, and that is the drug, Imuran, which is used in some types of autoimmune, proliferative disorders that involve inflammation of the liver. Imuran is an interesting example of some of the problems encountered in genetic uniqueness relative to oxidative liver injury. That has to do with the polymorphism of the enzyme methylthiopurine transferase, or MTPT. If a person is a slow metabolizer type and is given Imuran, it can be life threatening because of liver toxicity.

BB: I've seen that many times. In fact, I know people who have autoimmune hepatitis. They're doing very well. They have a positive ANA (anti-nuclear antibodies). They go to a hepatologist and they're put on Imuran and prednisone and they start degenerating very soon after that. When they come to our office, we have to wean them off those drugs and get them on a more sensible program.

JB: It was Dr. Helmut Sies who first coined the term "oxidative stress." He is the author of the book, *Hepatic Oxidative Stress*. That is the terminology we would apply to some of the conditions at the cell

biology level that you are describing. The cells in the liver are undergoing some kind of mitochondrial uncoupling, producing increased levels of oxidants that cause the redox potential of the cell to be overwhelmed, leading to oxidative inflammatory disorders. That relates in part to the pharmacogenomics of the individual, the basic genetic underpinnings. Do you find from patient histories that there are certain characteristics that make them more susceptible to some of the liver-related autoimmune or inflammatory disorders?

The Role of Emotional Stress in Liver Disease

BB: I always ask our patients a question when they first come in that most of them have never been asked—have you suffered any severe emotional stress over the past several years? This is especially so with hepatitis C patients. Almost all of them say yes—they had a divorce, or they lost a family member and were very depressed for a long time. I explain to them that they probably experienced high cortisol levels during that period of time and probably became immunosuppressed. Hepatitis C viruses, for example, might have been relatively dormant. When they're immunosuppressed, they become active and these people get sick. Then, I usually ask about their diets, such as how many vegetables they eat a day. It's really depressing to see how many Americans just eat meat and potatoes and fast food every day. Many of these people have very poor diets. Then, I ask if they use alcohol, smoke, and what their occupation is. If they are a house painter or a mechanic, they might be subjected to hepatotoxic solvents every day, which interferes with immunity. I take all of these things into consideration.

A paper was published several years ago, I think it was in 2000, by Seeff and Miller, where they studied patients with the hepatitis C virus (HCV) for 45 years.¹² They looked at thousands of HCV-positive patients. It seems that if these patients had decent lifestyles, took good care of themselves, and didn't drink and smoke, now they're in their 70s and 80s, and they don't even know they have liver disease. But the people that get sick are the ones that have gone through terrible stress and have poor lifestyles. It's the same old story over and over again with any disease. If people take good care of themselves, they seem to do very well. If they don't, they get sick.

JB: From the way you've described this, there seems to be a connection among hepatitis C and chronic diseases such as Epstein Barr or chronic fatigue or fibromyalgia syndromes. It seems that they cluster around similar etiological principles. Have you noticed any similarity among those conditions?

BB: It all seems to be like the chicken pox/shingles effect. I see it over and over again, even with cancer.

JB: You've extended your work with lipoic acid to look at other liver-specific protecting agents—antioxidants, or modulators of the inflammatory pathway. Have you found that other agents—silymarin, for instance—synergize or improve the activity of lipoate, or does it stand by itself?

Importance of B Vitamins

BB: Lipoic acid appears to be the rate-limiting factor for the production of energy from the mitochondrion. Carbohydrate or protein is eventually converted into pyruvate, but acetyl CoA is the food for the mitochondrion. What changes that pyruvate into acetyl CoA? There is the pyruvate dehydrogenase complex, but it doesn't work without the cofactor, alpha lipoic acid. It seems that when people are young, they seem to produce plenty of lipoic acid and they get plenty of energy out of their mitochondrion. But when people become ill or get older, they produce less alpha lipoic acid and they have less energy. They get a less efficient mitochondrion and a sick cell. What goes on during this period? Well, you lose a lot of the B vitamins, the B complex vitamins. They're depleted in this process. For example, thiamine, niacin,

biotin, and others, too. We always include a sufficient dose of B complex vitamins when people are taking alpha lipoic acid. I know Dr. Will Taylor from the University of Georgia and his work with selenium. From what I get out of his work, it seems that these viruses, the retroviruses such as HIV and hepatitis C, and perhaps all viruses, seem to, in one way or another, monitor selenium levels. When selenium levels go up to a certain point, even though the virus is probably not an organism but just an infectious chemical, it thinks the person is healthy. But when selenium levels go down, a virus thinks the person is sick and starts replicating. Therefore, we always give 200 mcg of selenium twice a day to people with liver disease. In many cases, it seems to keep the hepatitis C virus in check.

Use of Silymarin to Treat Liver Disease

Back in the 1970s when Dr. Bartter and I were visiting scientists at the Max Plank Institute, we learned about silymarin, the extract from milk thistle. We always add 300 mg of silymarin, four to six times a day to the regimen because we know that it protects the liver cells from further damage and it's a great antioxidant, too. That's what we do for hepatitis C.

A Case History of Metastatic Prostate Cancer

Eight years ago, I had an unusual experience. A man came into our office with metastatic prostate cancer. He also had lupus and rheumatoid arthritis. He had been to one of the large medical centers and they told him that he was going to die; the prostate cancer was in his bones; there was no hope; he was finished, and he had only a few months to live. He came into my office asking me if I could help him nutritionally and that if he was in bad pain, could I possibly give him some narcotics. I said I'd be glad to help him and told him I had some ideas. He asked me if I'd ever heard of Dr. Bernard Bihari in New York and I said that I hadn't. He heard that this doctor cured somebody with metastatic prostate cancer and asked me what I thought about that. I told him he should get right up there to see him, and he did.

I didn't see the man for probably three years. Finally, he came in and looked good. I asked him how he was doing and he said he had sinus trouble. This area of the southwest has a lot of blowing dust this time of the year and many people suffer from bad allergies that eventually turn into sinusitis and create problems. I asked him about his prostate cancer and he told me it was cured. His PSA went from about 12 down to 0.1. Then I asked him about the lupus and rheumatoid arthritis. He said that was gone, too. I asked him what he was doing. He told me Dr. Bihari put him on low-dose naltrexone. Are you familiar with that?

JB: Yes. It's a beta endorphin-blocking agent.

Naltrexone and Liver Disease

BB: Just a very small amount—3 mg at bedtime—seemed to cure the whole problem. It seemed to control the lupus and the joint pain. I started putting our people with autoimmune disease, our lupus patients, on this at bedtime and weaning them off methotrexate and prednisone. We have about 60 of them and they've gone from very sick people on very dangerous drugs to completely normal, healthy people. I thought that it worked for autoimmune diseases like lupus, it will probably work for autoimmune hepatitis and primary biliary cirrhosis. I started all of our autoimmune hepatitis and biliary cirrhosis patients on it and got the same fantastic results.

We added that to our autoimmune regimen.

JB: That is a great clinical pearl. Have you had a chance to speculate on the mechanism of action, or is it still open for discussion?

BB: The more I learn, the less I know. And the older I get, the more I realize that I really don't understand everything that's going on, but I think what it does is modulate the immune system with autoimmune disease, and it's probably related to the opioid blockade and the release of endogenous endorphins. The immune cells, especially the Th1 cells, all have opioid receptors and I guess this just gooses them to start doing their work properly.

JB: That's a very exciting clinical observation. That's where great new breakthroughs come from—making these observations and then finding out how to reproduce them in other patients. Thank you so much. It's fascinating to hear about the evolution of your story and observations. In May of 1997, I interviewed Dr. Will Taylor on FMU about his work on selenium and HIV aids, and the whole viral spectrum and its relationship to selenium. That's another chapter in this ongoing saga. To reconnect with you nine years after our initial interview and examine the evolution of your clinical concepts, adding the naltrexone wrinkle, shows how good observers and clinicians can continue to refine and evolve the success of their therapies.

As I mentioned in the introduction today, in 1996, when I first interviewed you, the feedback from the listeners about the experience they had in applying your concepts was absolutely remarkable. It sounds like we've added another level to that, and I'll be anxious to see how it's received by the clinicians in our audience. Thank you, Dr. Berkson, for being the observer and the clinician that you are, and for your willingness to share time with us. I can assure you this news is going to spread far and wide. I want to thank Dr. Berkson for his very informative talk. It added to the substance of the interview we had with him on FMU in 1996. We continue to learn old things in new ways.

Naloxone in the Treatment of Autoimmune Disease

One of the things Dr. Berkson mentioned that I want to follow up on is the association of naloxone with the treatment of autoimmune disease. That was an interesting "aha" for me, and I would like to add a couple of thoughts about why that seems reasonable from a biomedical perspective.

The naltrexone molecule, and the related molecule naloxone, block the mu opioid receptor and the methionine-enkephalin (met-enk) receptor associated with endogenous analgesia. If you use something that blocks those receptors, it seems that it would increase pain and disability, rather than lower them because they are the endogenous opioid receptors. There is a story I would like to share with you that comes out of the observations that Dr. Berkson shared with us. It goes back to Nobel Prize-winning work from Sune Bergstrom's laboratory at the Karolinska Institute in Sweden. Unfortunately, Dr. Bergstrom passed away in August 2004 at the age of 88. He won the Nobel Prize in Medicine and Physiology in 1982 after isolating and elucidating the chemical structure of prostaglandins. He was the first person to study the physiology of prostaglandins. He and his colleagues have been actively involved in this research at the Karolinska Institute for many years. They spawned literally thousands of scientists that have been working in this field. Two of those scientists, still members of the Karolinska faculty, are Bengt Samuelsson (a co-recipient of the Nobel Prize) and John Vane, who eventually demonstrated aspirin's mechanism of action. This is one of the premier centers in the world for research on inflammation.

The group at Karolinska, with Dr. Bergstrom as one of the contributors, looked at the effect of naltrexone on met-enk-induced bone loss. Bone loss, or osteoporosis, is, in part, a bone inflammatory disorder. In the *Journal of Bone Mineral Research* in 1998, this group published a paper that looked at the role of met-enk inhibition in osteoblastic function.¹³ Osteoblasts are the bone cells involved with bone reformation. It turns out that met-enk levels, these endogenous opioids, inhibit osteoblast growth and function. Naltrexone blunts the effect of met-enk and allows the osteoblast cells to continue to grow and function in cell culture assays. By blunting the met-enk activities in bone cell, using naltrexone, osteoblastic osteogenic activity may be preserved.

Etiology and Treatment of Hepatitis

That is somewhat of a departure from the concept of autoimmune disease, but consider that perhaps Dr. Bergstrom's observations are not that paradoxical. I want to talk specifically about hepatitis and its induction by viral infections, chemicals, or alcohol.

One of the intercellular molecules, Fas, a CD95 protein, induces hepatocyte apoptosis in cytotoxic activity related to neutrophils that are infiltrating the liver. These are major events leading to what we clinically call hepatitis. It has been reported that endogenous and exogenous opioids, particularly morphine-like derivatives, via direct interaction with Fas CD95, sensitize splenocytes to Fas-mediated apoptosis and upregulate FAS messenger RNA formation. That subsequently modulates white blood cell neutrophil activity (cell-mediated defense), which causes hyperreactivity with liver tissue leading to an injured liver through oxidative stress and the release of hypochlorite and other oxidants. This is a Fas-induced hepatocyte apoptotic process associated with cirrhosis.

The most interesting part of this story is that it has recently been shown that blocking the opioid receptor with low doses of naltrexone reduces liver damage and consequently increases the survival rate of animals after they were administered a liver-injury substance. This was reported in the *Journal of Hepatology*.¹⁴ It appears that there is no association between hepatotoxicity and naltrexone, and it appears to very effectively influence the reduction of acute viral hepatitis, according to a recent review published in the journal, *Addiction and Biology*.¹⁵ The authors state that during the past decade, naltrexone has been shown to be safe and effective in the treatment of pruritis associated with severe jaundice caused by severe and sometimes life-threatening cirrhosis and other liver diseases. This amplifies and supports the point made by Dr. Bergstrom.

On the other side of the coin, a person taking morphine, which activates these mu and met-enk receptors, enhances hepatitis C virus replication. A paper in the *American Journal of Pathology* reports the ability of a morphine drug to increase hepatitis C virus replication *in vitro*.¹⁶ This appears to occur through the pathways I was describing earlier, through the mu receptors. Both alcohol and morphine will enhance hepatitis C replication through those processes.¹⁷ Naltrexone appears to block those activated processes through the mu receptor, which may interfere with liver injury.

We are learning about how some of these environmental agents work through liver signaling processes that are connected to opioid receptors on liver cells, particularly the embedded white cells in the liver, and blocking them with naltrexone or one of the opioid receptor antagonists, can have positive influence on the course of liver recovery. Obviously, we want to remove the precipitating factors—alcohol and/or

morphine—but we want to decrease liver oxidative injury and apoptosis.

In his discussion, Dr. Berkson talked about the use of lipoic acid, silymarin, and selenium. He spoke about Will Taylor's work on selenium and its activation of antiviral effects. He also talked about low-dose naltrexone, 3 mg at bedtime, for patients with autoimmune disease. We are talking about the reduction of hepatic toxicity, the interrelationship between glutathione levels in the liver induced by N-acetylcysteine and/or lipoic acid protection. Naltrexone plays a role in preserving those pathways for glutathione synthesis in the liver, as well. This has been reported in the *Journal of Pharmacology and Experimental Therapeutics*.

Treatment of Primary Biliary Cirrhosis

What about specific examples of the use of naltrexone for the treatment of primary biliary cirrhosis? There is a good review that was published last year in the journal, *Drugs* that discusses the role that various medications have in the induction of primary biliary cirrhosis through upregulation of hepatic oxidative injuries.¹⁹ The endogenous opioid receptor antagonists, such as naltrexone, may be effective for lowering pruritis and inflammatory conditions associated with autoimmune hepatitis.

Dr. Bergstrom left us with a powerful vision for a field that needs some help. The agents we are using today, such as interferon and Imuran, are not the answer to the problem, particular in the area of chronic liver disease. The functional hepatology argument—environmental factors, genes, and diet—is where the solution may emerge, because the gut delivers a lot of its messages to the liver. The liver picks up those messages and transmits inflammation to the rest of the body. Dealing with this as a system at the functional level may provide a much better solution for remediation of the excessive 3 billion dollars of healthcare expenditures that occur every year because of chronic liver disease.

I hope we have given you some new information of interest this month. We look forward to being with you in August.

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