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Biosketch

Herbert L. Bonkovsky, M.D., is a tenured Professor of Medicine and Molecular Medicine & Translational Research and Chief of Hepatology at Wake Forest University/NC Baptist Medical Center, Winston-Salem, NC. Dr. Bonkovsky also has academic appointments as Visiting Professor at Winston-Salem State University, Professor of Medicine, at The University of CT Health Center, and Professor of Biology and Medicine at the University of North Carolina. Dr. Bonkovsky is known nationally and internationally as a clinical hepatologist, teacher, mentor, and clinical investigator. He is a valedictory graduate of Earlham College [Richmond, IN] and Case Western Reserve University School of Medicine [Cleveland, OH]. His Post-graduate training was at Duke University, Case Western Reserve University School of Medicine, The U.S. National Institutes of Health, Dartmouth Medical School, and Yale University.

Dr. Bonkovsky formerly served as Director of the Division of Digestive Disease and Nutrition at the University of Massachusetts Medical School and as Director of the Office of Clinical Research and the General Clinical Research Center and Director of the Liver- Biliary-Pancreatic Center at the University of Connecticut Health Center. He was recruited to Carolinas HealthCare System [CHS}, Charlotte, NC, from U Conn in 2007 and, for 5 years, served as VP for Research at CHS. Dr. Bonkovsky has continued to maintain an active clinical practice, focused on liver disorders and metabolic disorders, especially disorders of iron, porphyrin, and heme metabolism. His currently funded research is in porphyrin and heme metabolism, effects of heme and iron on gene expression and intermediary metabolism, and drug- and herbal supplement-induced liver injury.

Among Dr. Bonkovsky's seminal contributions to the study of disorders of porphyrin and heme metabolism were the first preparation and therapeutic use of heme [in the form of the hydroxide, hematin] for therapy of acute porphyrias and demonstration of defective activity of ferrochelatase as the underlying cause of erythropoietic protoporphyria. Hemin for human use was the first Orphan Drug ever developed, and its use for therapy of acute porphyric syndromes has stood the test of time. Still today, it is the treatment of choice for treatment of attacks of acute porphyria.

Dr. Bonkovsky also played a key role in establishing the programs in liver transplantation both at Emory University and at U Mass Medical Center. He also was a founding
member of the Liver Center at Carolinas HealthCare System, Charlotte, NC, where he served for several years as VP and Director of research. He was recruited to Wake Forest to continue with his funded research and to help build up subspecialty expertise and services in hepatology, with emphasis upon diseases of metal metabolism, such as hemochromatosis, hypoceruloplasminemia, Wilson's disease, and the porphyrias. The Liver Clinics at Wake Forest Baptist Medical Center also evaluate and manage patients with the more commonly occurring liver diseases, such as viral hepatitis, alcoholic and non-alcoholic fatty liver disease, and auto-immune liver disorders [such as autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis]. Dr. Bonkovsky also serves as chief of the Liver, Digestive, and Metabolic Disorders Laboratory of Wake Forest, which has competed successfully for external funding from NIH [NIDDK, NHLBI] and from Foundations and Societies. In the past 6 years, Dr. Bonkovsky has filed five patent applications for new therapies and diagnostic tests for viral hepatitis and neuro-muscular diseases.

Dr. Bonkovsky is a member of many learned and professional societies: he is a Fellow of the American College of Gastroenterology, the American College of Physicians, the American Gastroenterological Association, and the American Association for the Study of Liver Diseases. He is also an elected member of the American Society of Clinical Investigation and the Association of American Physicians. Continually since 1996, Dr. Bonkovsky has been selected by his peers as one of America's Top Doctors and Top Gastroenterologists and Hepatologists. Dr. Bonkovsky is author or co-author of more than 360 presented abstracts, 40 brief reports, 40 books or book chapters, and 380 original papers.

Abstract: DILI caused by anti-TNF agents

TNF-alpha [TNF] is a cell signaling protein involved especially in inflammatory responses. It is a cytokine and an acute phase reactant, produced chiefly by macrophages, including von Kupffer cells of the liver. It is also produced to lesser extents by numerous other cell types, including eosinophils, hepatocytes, CD 4+ and NK lymphocytes, mast cells, neurons, and PMNs. The TNF gene is located at chromosome 6 p21.3 and is comprised of four exons and three introns. The protein product primarily is a 223 amino acid type 2 transmembrane protein, existing chiefly on cell membranes as homotrimers. A soluble form of 51 kDa is released from membranes by action of a metalloprotease called TACE or ADAM17. TNF acts on cells chiefly by binding to two receptors, called TNFR1 and TNFR2. Such binding leads to signal transduction through three main pathways, namely, NF-kB, MAPKs, especially JNK, and a death pathway.

TNF levels are increased in numerous chronically inflammatory diseases, including ankylosing spondylitis, inflammatory bowel disease [in which ankylosing spondylitis may occur], psoriasis and its arthritis, rheumatoid arthritis, and others. Studies performed during the past ~ 20 have shown that such disorders often respond dramatically to anti-TNF agents, the first of which was infliximab, a human-mouse chimeric monoclonal antibody. Others that also have proven effective and are currently approved for use in the USA include etanercept, adalimumab, certolizumab, and golimumab. Anti-TNF agents have markedly improved the quality of life for thousands of patients, but they are not without adverse effects, including reactivation of HBV and TB, increased risks of other infections, lymphomas, demyelinating diseases, skin rashes, and DILI. DILI due to anti-TNF agents has been reported most often due to infliximab [79% of 107 reported cases]; less often adalimumab [15%] and etanercept [6%] have been implicated. 57% of reported cases have occurred in women, among whom 65% developed features of autoimmune disease with elevations in ANA, ASMA, etc. Those with AI features have had significantly higher median levels of serum ALT at presentation [711 vs 446 IU/L] and longer latencies [20 vs 12 weeks]. Clinical presentations are widely varied with some patients presenting with sever and prolonged cholestasis. The latency has varied greatly, from DILI occurring after a single dose of anti-TNF agent to as long as 156 weeks after starting the agent. However, the median latency is about 16 weeks. The treatment is prompt cessation of the offending agent. Corticosteroids have been used, but it is uncertain whether they influence the course of disease favorably or not. Fortunately, after the drug has been stopped, patients generally recover; only one patient [with pre-existent cirrhosis] has required liver transplantation. Some patients later re-challenged with the same or another anti-TNF agent have again developed DILI with a more accelerated course; re-challenge with the same agent is not recommended. If another agent is used, there should be very close and careful follow-up, especially during the first 24 weeks of resumed therapy. The pathogenesis of DILI due to anti-TNF agents is not well understood, but immune responses, both antibody and T-cell dependent appear most likely. A host immune response to the chimeric human-mouse infliximab seems to occur more frequently and more likely to lead to DILI.