



21st Annual Harvard Nutrition and Obesity Symposium

June 30th, 2020

NAFLD

**Nutrition
Obesity
Research
Center at
Harvard**



**@HarvardNORC1
#NORCHNAFLD
#NAFLDSymposium**

Nonalcoholic Fatty Liver Disease (NAFLD): Mechanisms and Novel Therapeutics

Presented by:



With additional unrestricted educational support from Theratechnologies, Inc., and Intercept Pharmaceuticals



Schedule:

Welcome and Introductions

8:00 AM *Steven Grinspoon, MD*
Harvard Medical School

Global Burden of NAFLD and NASH

8:15 AM *Zobair Younossi, MD*
Inova Fairfax Medical Campus

Session I: Mechanisms

Moderator, *Laura Dichtel, MD, MHS* (Harvard Medical School)

8:50 AM George L. Blackburn Lecture: Insulin Resistance and NAFLD
Sudha Biddinger, MD, PhD
Boston Children's Hospital

9:40 AM Human Genetic Insights into NAFLD
Elizabeth Speliotes, MD, PhD, MPH
University of Michigan

10:15 AM BREAK

10:45 AM Obesity, Adipocyte Dysfunction, and NAFLD
Jeffrey Schwimmer, MD
University of California, San Diego

11:20AM The Microbiome and Fatty Liver Disease
Bernd Schnabl, MD
University of California, San Diego

12:00 PM BREAK

12:20 PM NAFLD Natural History and a NAFLD Simulator
Jagpreet Chhatwal, PhD
Harvard Medical School



Schedule:

Session II: Therapeutics

Moderators, *Raymond Chung, MD* and *Kathleen Corey, MD, MPH, MMSc* (Harvard Medical School)

1:00 PM NAFLD and CVD

Kathleen Corey, MD, MPH, MMSc

Harvard Medical School

1:35 PM Targeting Metabolic Pathways to Treat NAFLD

Arun Sanyal, MD

Virginia Commonwealth University

2:10 PM Targeting Endocrine Pathways

Steven Grinspoon, MD

Harvard Medical School

2:45 PM BREAK

3:15 PM Targeting Inflammatory & Fibrotic Pathways

Mary Rinella, MD

Northwestern University

3:50 PM Nutritional Modification to Treat NAFLD

Miriam Vos, MD, MSPH

Emory University

4:25 PM Clinical Burden and Future Directions, Including Relevant Endpoints

Manal Abdelmalek, MD, MPH

Duke University

5:00 PM Wrap-Up: Non-Invasive Assessment of NAFLD

Rohit Loomba, MD, MHSc

University of California, San Diego

5:30PM Adjourn

Steven Grinspoon, MD

Harvard Medical School



Speakers and Moderators:

Manal Abdelmalek, MD, MPH

Professor

Duke University

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Clinical Burden and Future Directions, Including Relevant Endpoints

Sudha Biddinger, MD, PhD

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George L. Blackburn Lecture: Insulin Resistance and NAFLD

Jagpreet Chhatwal, PhD

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NAFLD Natural History and a NAFLD Simulator

Raymond Chung, MD

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Co-Moderator for Session II: Therapeutics

Kathleen Corey, MD, MPH, MMSc

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NAFLD and CVD and Co-Moderator for Session II: Therapeutics

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Moderator for Session I: Mechanisms

Steven Grinspoon, MD

Professor of Medicine, Massachusetts General Hospital/Harvard Medical School

Chief, Metabolism Unit, Endowed Chair in Neuroendocrinology and Metabolism

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Targeting Endocrine Pathways



Rohit Loomba, MD, MHSc

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Wrap-Up: Non-Invasive Assessment of NAFLD

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Targeting Inflammatory & Fibrotic Pathways

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Targeting Metabolic Pathways to Treat NAFLD

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The Microbiome and Fatty Liver Disease

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Obesity, Adipocyte Dysfunction, and NAFLD

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Human Genetic Insights into NAFLD

Miriam Vos, MD, MSPH

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Nutritional Modification to Treat NAFLD

Zobair Younossi, MD

Chairman, Department of Medicine

Inova Fairfax Medical Campus

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Global Burden of NAFLD and NASH



Webcast:

The Symposium will be webcast for registered applicants at:

http://healthcare.partners.org/streaming/Live/MGH/2020.06.30_NAFLD_Symposium.html

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The National Institutes of Health—National Institute of Diabetes and Digestive and Kidney Diseases

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The George L. Blackburn Foundation for Nutrition Medicine

Chairman Bruce R. Bistrian MD, PhD, MPH

Steven Heymsfield MD

Thomas Jaksic MD, PhD

Daniel Jones MD, MS

Scott Shikora MD



Memorial for George Lincoln Blackburn MD, PhD

George Lincoln Blackburn was born on February 12, 1936 in McPherson, Kansas to George Blackburn, who ran a company that sold farm equipment, and Betty Warick. He was raised in Joplin, Missouri. He died February 20, 2017 of melanoma. Dr. Blackburn filled those 81 years with grace and infectious humor that endeared him to so many. He had a life-long singular focus on the essential role that nutrition plays in public health and clinical medicine.

Dr. Blackburn graduated from the University of Kansas in 1958 with a BA in Chemistry. He then took an interim break for U.S. Navy service as a Lieutenant, of which he was very proud, after which he received his medical degree as AOA from its Medical School in 1965. On completion of his surgical residency on the Harvard (Fifth) Surgical Service at Boston City Hospital, (which included the New England Deaconess Hospital as a training site), he was appointed as Instructor in Surgery. George served as the surgical ICU director while also completing a 3 year NIH fellowship at MIT. He was awarded a PhD in Nutritional Biochemistry and Metabolism in 1973. During this period the Fifth Surgical Service moved to the New England Deaconess Hospital where Dr. Blackburn spent the remainder of his career.

Dr. Blackburn's medical career coincided with major advances in clinical nutrition that would transform the field. The initial discovery in 1968 of the means to nourish humans by the parenteral route through total parenteral nutrition (TPN) by Stanley Dudrick and Douglas Wilmore, (a medical school classmate of George's), is widely acknowledged to be one of the major medical breakthroughs of the 20th century. Critically ill patients with temporary loss of intestinal function could avoid the consequences of developing protein calorie malnutrition (PCM) and its morbid complications including even death from starvation. However, it was George and his colleagues who several years later first documented the astonishingly common prevalence of moderate and severe PCM, often exceeding 50% of hospitalized adults that established the true extent of the problem. A system of nutritional assessment was developed by George and colleagues that defined patients most likely to benefit from invasive nutritional support in the form of TPN, enteral nutrition, or the combination of both. The presence and severity of PCM was determined by upper arm anthropometry, serum albumin and transferrin levels, immune competence by delayed hypersensitivity skin tests, a creatinine height index developed by them, 24-hour urine urea nitrogen excretion to estimate nitrogen balance and metabolic stress originated by them, and estimates of recent weight loss, physiologic impairment, and recent protein and energy intake.

To address the many early challenges of TPN including a high infectious risk took a multi-pronged approach to which George made many contributions. On the one hand, George and colleagues pioneered the development of new components of TPN including novel fats, some naturally occurring and some artificially constructed, including medium chain triglycerides, structured lipids, and fish oil, novel carbohydrates like xylitol, and unique amino acid formulations such as branched chain amino acids that made TPN more effective and often safer. An important contribution to reducing the risks of TPN while preserving and even enhancing its benefits was their identification of the salutary impact of dramatically reducing the daily energy provided, particularly as carbohydrate, which was initially considered essential by its inventors. Reducing the amount of carbohydrate and total energy reduced the incidence of hyperglycemia and its infectious risk. To offset partially the reduction in energy they increased the protein intake to improve nitrogen economy. For a much smaller group of patients with permanent loss of intestinal function rendered insufficient to sustain life, chronic home TPN was truly life-saving and offered the opportunity to lead a long and productive life. George and colleagues developed one of the first home TPN programs nationally which was the regional referral program in New England for many decades. George and colleagues made similar contributions to enteral nutrition. They identified two components,



fish oil and structured lipids of their design, that could improve clinical outcome by reducing infection rates and improving organ function in the critically ill. These nutrients remain in clinical use worldwide.

With his medical colleague, Bruce Bistrian, (with whom he collaborated throughout his career), they conducted basic research into PCM identifying the interaction of nutrition and inflammation as the primary factors determining the type of PCM that developed. They were the first to identify the protein catabolic consequences of the pro-inflammatory cytokines, interleukin 1 and tumor necrosis factor, employing stable and isotopic tracers of amino acid metabolism in animals and man. They showed that the systemic inflammatory response mimicked by cytokine infusion increased the protein catabolic rate in the well-nourished, that PCM reduced the ability to mount an inflammatory response which was harmful. and that short-term feeding could restore this responsiveness and improve clinical outcome in both animals and humans. These studies underpin the bedrock principles in determining which patient is likely to benefit from invasive feeding in the acute care situation, the estimated amount of initial lean tissue loss, the adequacy of feeding, and the intensity and likely duration of the systemic inflammatory response.

However, these major developments would have had limited application without the training of physicians, surgeons, pharmacists, dietitians, and nurses in the application of this knowledge. George initiated the first multidisciplinary nutrition support services at both the Boston City Hospital and the New England Deaconess Hospital. This model remains the ideal in the developed world today. To provide physician training a fellowship in parenteral and enteral nutrition was initiated with hospital backing, with NIH training fellowship support, and a three-decade collaborative exchange with the Royal Aberdeen Infirmary in Scotland. This promotion of physician training in nutrition was George's enduring aim as exemplified by his founding role in the American Society for Parenteral Nutrition (ASPEN) where he served as the 2nd President. He also served as President of the Obesity Society, the American Society for Clinical Nutrition, as well as his long service with the American Society of Nutrition.

The other common form of malnutrition is the dramatic increase in obesity rates over the past 4 decades. George's initial involvement arose from his PhD thesis. The focus of this research was to determine in normally nourished subjects undergoing surgical treatment whether providing isotonic amino acids by peripheral vein over the short-term would preserve lean body mass and body function better than dextrose in water. D5W was the conventional therapy based on earlier work with the "life raft" ration performed in the 1940's by the noted Harvard physiologist, James Gamble. Seeking an experimental model, George recruited obese adults. In MIT's Clinical Research Center, these subjects consumed only small amounts of meat and no calorie liquids to create a state of modified fasting. In collaboration with Bruce Bistrian, they determined the amount of dietary protein, 1.5 g/kg ideal body weight, along with RDA amounts of vitamins and minerals to make the diet nutritionally complete save for energy. This diet could maximize fat loss with essentially 100% lean tissue preservation as demonstrated by daily nitrogen balance, whole body protein turnover studies using ¹⁵Glycine or ¹³Leucine as tracers, and whole body ⁴⁰K counting for body composition estimates. The difficulty of maintaining weight loss, particularly in the morbidly obese, fostered an interest in gastric bypass surgery that was pioneered by Edward Mason at the University of Iowa to replace the previous procedure, the jejunio-ileal bypass, which often led to unacceptable metabolic complications. George was the surgeon for the 1st gastric bypass in New England and largely responsible for making The New England Deaconess and subsequently, the Beth Israel Deaconess Medical Center a major center for this procedure. An important research contribution was his demonstration of preservation of lean tissue with weight loss by whole body ⁴⁰K counting. George's vision spearheaded best practice standards for these metabolic surgical procedures emphasizing patient safety and quality of care. In 2005 he was the Vice Chair of the Commonwealth of Massachusetts Betsy Lehman Center for Patient Safety and Medical Error Reduction Expert Panel on



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Weight Loss Surgery and in 2009 he chaired the expert panel that updated recommendations for best practices. In partial recognition of his substantial pioneering contribution to the field and to the program at Beth Israel Deaconess Medical Center, the Department of Surgery honored him by naming the Bariatric Surgical Service the Blackburn Service in 2014.

Dr. Blackburn also touched the lives of many through his contribution to the medical treatment of obesity. He co-developed the protein-sparing modified fast (PSMF) and was a principal investigator in an NIH sponsored trial of the use of the PSMF, behavior modification, and exercise in obese hypertensive subjects. He was also an investigator in the NIH Look AHEAD trial, the longest and largest randomized control trial of behavioral intervention on weight loss. His enduring legacy may also derive from his educational endeavors among physicians through his development and direction of 4 annual Harvard CME programs, Practical Approaches to the Treatment of Obesity (1986-2011), Basic and Advanced Courses of Malnutrition in Hospitalized Patients (1977-1998) and Parenteral and Enteral Nutrition (1998-2010). He also is credited with creating 2 stand-alone courses that shared the findings of the Betsy Lehman Center and promoted national accreditation, the International Patient Safety in Obesity Surgery in 2005 and Implementing Accreditation Standards and Best Practice in 2009.

At the time of his death Dr. Blackburn was the S. Daniel Abraham Chair of Nutrition Medicine, Professor of Surgery, and Associate Director of the Division of Nutrition at Harvard Medical School, Founder and Scientific Director of the Center for the Study of Nutrition Medicine in the Department of Surgery at Beth Israel Deaconess Medical Center and Associate Director of the Boston Nutrition Obesity Research Center. His honors included the Grace Goldsmith Award from the American College of Nutrition in 1988, Goldberger Award in Clinical Nutrition from the American Medical Association in 1998, and as Master of the American Board of Obesity Medicine Recognition Award in 2013. To commemorate his exemplary career and numerous contributions Friday, April 21th, 2017 was proclaimed George Blackburn Day by Governor Baker, and an endowed Chair in Innovation in his name has been established at the Beth Israel Deaconess Medical Center and Harvard Medical School.

For those of us who worked closely with Dr. Blackburn, he was blessed with the ability to bring out the best performance and thinking from colleagues, fellows and students. He also had an uncanny knack to find nuggets of gold (unique information) from what otherwise seemed to be common soil (routine research observations) in his own work and that of others. His research productivity is testament to this skill. He also practiced what he preached, walking up the 8 flights of stairs to his hospital office each day into his 80's and encouraging others to accompany him. Above all else, he had a vision that nutrition science was an important component of clinical medicine that could dramatically impact human health and well-being, and that clinicians should be made aware of and incorporate this basic message into their practice.

In summary, George's accomplishments were extensive and wide ranging including the protocol for nutritional assessment of hospitalized patients, the initial establishment of the multidisciplinary nutrition support service, the many refinements in TPN and enteral practice to improve safety and effectiveness including the development of novel nutritional substrates, the seminal work in the foundation of effective medical treatment for the moderately obese and safe and efficacious surgical treatment for the severely obese. George had an extraordinary commitment and accomplishments in medical education that largely created the field of nutrition medicine. After more than 50 years of contributions, we will miss his wise counsel and incredible mind. He will truly be remembered as a great physician and surgeon who advanced ideas, knowledge, and policy for the benefit of future generations with humility and kindness. There are many clinicians world-wide that he trained who now carry a little of George with them to work every day. He truly was a giant of a man and it will be a long time before we see another one like him.