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Forewords

From the Editor-in-Chief

In July 1966, I reported to my first duty as an officer in the United States Public Health Service, assigned as a Clinical Associate at the National Institutes of Health to the laboratory of Dr. Donald Fredrickson in the NHLBI. I had interviewed several months before and was warmly welcomed by Dr. Robert Levy, who had worked with Dr. Fredrickson for the previous three years also as a Clinical Associate. Bob, as we all called him, had decided to remain on the staff after finishing his tour of duty as a PHS Officer to head a section of the Molecular Disease Branch under Fredrickson. Bob became my mentor on a daily basis and in his initial guidance, gave me a list of publications that were meant to bring me up to date in the world of plasma lipid transport. The first of the papers contained some 80 pages published in a journal that I had never heard of called *Plasma*.[1] As he handed it to me, Bob Levy said: (paraphrasing) "This paper by John Gofman contains almost everything we know about the blood plasma lipoproteins and their relation to disease. " It was filled with tables and a few diagrams and used terminology that was totally unfamiliar. To do this work, the Gofman laboratory at the University of California, Berkeley, used a very difficult method called analytical ultracentrifugation. Bob continued stating that the Fredrickson laboratory was attempting to provide an analysis of the several lipoproteins defined by Dr. Gofman using a more rapid method, one virtually any laboratory could adopt. That method was paper electrophoresis of plasma followed by staining of the lipoproteins with a lipophilic dye called oil red O. This technique led to many paper strips (about 1-1/2 by 8 inches), crossed by red bands hanging around the laboratory. The patterns were used to phenotype the patients, assigning a numerical designation (Roman numerals) I through V. This led to a series of studies using a mixture of qualitative (electrophoresis) and quantitative analyses (precipitation and preparative ultracentrifugation) that produced the typing system of Fredrickson, Levy and Lees.[2] Studies involving hundreds of patients were published at the end of 1966 and in the beginning of 1967 in the *New England Journal of Medicine,* with strong evidence that these were often familial characteristics suggesting major gene defects. Elevated beta-lipoprotein was known to characterize familial hypercholesterolemia, and this disorder was well known to predict early onset of vascular disease. This ability to define the lipoproteins with methods that were relatively easily established accelerated the era of lipidology. However, it was the work of John Gofman that truly defined the lipoproteins and gave birth to this field. As with many true breakthroughs, there was little initial acceptance. Most found it very hard to give up old concepts and to accept the complexity revealed in his experiments. Gofman struggled for several years to enlighten the investigators of the time, but finally returned to his initial interest of radioisotopes and their interaction with biological systems.

The Gofman Laboratory was a part of the Donner Laboratory of Medical Physics, Division of Medical Physics, Department of Physics and the Radiation Laboratory, on the Berkeley campus. He received his PhD in Physics and began working on heavy metal isotope isolation as part of the World War II effort to create nuclear fission. He was the first Post Doctoral fellow of Glenn T. Seaborg, and with Dr. Seaborg isolated Uranium 233, proving it to be fissionable and fitting into a formula to predict this property of large atomic nuclei. He was the first to isolate Plutonium in significant amounts for the early experimentation of this fissionable isotope. It was in these isolation efforts that he became facile with the ultracentrifuge. After the war, he entered medical school at the University of California, San Francisco, and returned to the laboratory to apply his ultracentrifugal skills to biological questions. The study of human plasma with his first post-doctoral fellow, Frank T. Lindgren, led to the realization that components of the blood that floated under high force fields in the analytical ultracentrifuge were lipoproteins, floating because of the relatively low density of their lipid component. A series of papers followed between 1949 and 1956 defining the composition of these particles in humans and rabbits under various experimental conditions. Our current terminology used to describe plasma lipoproteins was born in these experiments, thus VLDL, LDL, HDL2 and HDL3 were terms first used by John Gofman and his research associates. The paper in *Plasma* in 1955 summarized much of this work, lifting out the key findings of this

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work derived from studies of human plasma. The journal *Plasma* was only published for two years (1954 and 1955). Therefore, the paper that covered some six years of work relating concentrations of plasma lipoproteins to disease states in humans essentially disappeared from the literature. During a casual meal with Dr. Richard Havel at the International Atherosclerosis Meeting in July 2006, we discussed the importance of the Gofman contributions to our field and the seminal work reported in his 1955 manuscript. We agreed that it should be made available to our colleagues as an educational piece, and, furthermore, it was past time to give Dr. Gofman some well-earned recognition for the very important work that he had done so many years ago. It seemed particularly important since he is now 88 years old and not in the best of health. On my return home, I started a search for this publication. Havel thought he had a copy but could not locate it. Tom Bersot and his extremely helpful secretary, Sylvia Richmond, were able to locate a copy of the 1955 volume of *Plasma* in the Physics Library at Berkeley. They were able to obtain permission to send it on loan, from the Berkeley Library, to Elsevier in New York. There, it was possible to make satisfactory reproductions for accurate resetting of the type and reproduction of the figures. The result is its republication with the author's permission in this issue of the *Journal of Clinical Lipidology*.

Dr. Havel has provided a prologue to the article. As a faculty member at UCSF School of Medicine, he has known Dr. Gofman for many years. One of Dr. Havel's earliest papers utilized the Gofman findings as to the boundaries of density defining the major lipoprotein groups, to devise a scheme allowing the preparative isolation of these lipoproteins in quantities sufficient for detailed structural and compositional studies.[3] Through the efforts of another long time friend and editorial assistant, Ms. Egan O'Connor, we were able to obtain pictures of Dr. Gofman in his laboratory (cover photograph and Havel article) during the 1949 to 1956 period.

I hope you take the time to carefully read this document as both a scientific tour de force and a historically important presentation of concepts that underpin our field. I was most impressed on rereading the document that he not only discovered relationships previously unknown but defined important questions that remain unanswered even today. The importance of VLDL as a risk factor, the notation that diabetics are frequently marked by higher VLDL levels, the rise in atherogenic lipoproteins in males at a much earlier age than in women, the changes produced by meals and by heparin injection were rediscovered later without credit to this work. One of the mysteries that persist is his repeated finding that HDL has little predictive value when these lipoproteins are quantified with the ultracentrifuge. The very different finding of a highly predictive risk relationship associated with lower HDL cholesterol in later studies has never been reconciled.

Ms. O'Connor pointed out that one of the shortcomings of articles written in earlier times was the omission of the table of contents. She has graciously provided the Editor with a complete table of contents for the paper to follow. I hope you find this useful as you read the paper and as you return to it to compare notes with later publications which "discovered" the phenomena initially described by John Gofman. Once you have finished this paper and recognize that the lipoproteins initially were defined by their density characteristics and named by John Gofman, and that he recognized their clinical value, you will understand why the name of "Father or Clinical Lipidology" is fitting.

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