In Memoriam: Paul S. Roheim (1925–2008)

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Paul Samuel Roheim died on Wednesday, October 15, 2008, in Baton Rouge, LA. With his passing, we have lost a dear friend and a fine scientific colleague. I (G.S.) first met Paul in 1971 at a meeting of the American Heart Association. He was presenting a paper, and as soon as he opened his mouth I knew he was Hungarian, because his accented English sounded just like my Hungarian mother's. I approached him and we began a conversation that was to last for the next thirty-six years. When immigrants like Paul and I meet, the first question is always, "when did you come to the US?" If the answer is any time after 1945, the next question is, "how and where did you survive the war?" Paul, along with most Hungarian Jews, spent the year 1944–1945 in several German concentration camps. He mentioned that one of the camps was named Muhldorf-Waldlager, near Munich. Imagine the emotional scene when we discovered that both of us had been in Muhldorf at the same time. In fact, my father who was a physician in the camp, had saved Paul's life.[1]

After liberation by the US Army on May 2, 1945, Paul eventually found his way back to Budapest, where he graduated from the University of Budapest's Semmelweiss Faculty of Medicine in 1951. He chose a career in academic medicine and became an assistant professor of physiology in 1952 at Semmelweiss. Despite suboptimal conditions, Paul published several papers in Hungarian scientific journals. However, as the years passed, it became increasingly clear that Hungary under its communist government was an oppressive place to live and did not offer the opportunity to pursue a stellar career in medical research, nor were legal routes to emigration available. The Hungarian revolution in 1956 presented an opportunity to escape from Hungary. Paul grabbed it.

The Roheims (including parents and new wife) arrived in Philadelphia in 1957, where Paul spent a year in Hahnemann Medical College. Subsequently, he relocated to New York City, where he began his research career on lipoprotein metabolism at the Albert Einstein College of Medicine in

the Bronx. From his arrival in 1958 through his departure in 1976, Paul's research focused on lipoprotein and apolipoprotein metabolism. Upon relocating to New Orleans, he worked on apolipoprotein metabolism in mesenteric and peripheral lymph and in other biological fluids; he also conducted clinical translational research. In New Orleans, Paul directed the Division of Lipoprotein Metabolism and Pathophysiology in the Department of Physiology of the Louisiana State University Medical Center and he was also affiliated, as Adjunct Professor of Physiology, to the Division of Diet and Heart Disease at Pennington Biomedical Research Center, Baton Rouge, LA. On August 29, 2005, Hurricane Katrina struck New Orleans. Luckily, the Roheims had a timely evacuation and relocated to Baton Rouge. Unfortunately, Paul became progressively weak.

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[1] The Shoah Foundation Institute at The University of Southern California achieved an interview with Paul (Shmuayl Natan ben Moshe Yosaif) about his experience in the camp (interview #17783).

I (GLV) was introduced to Paul in the fall of 1972 by Professor Amadeo D'Adamo, and I gladly entered the world of lipoprotein metabolism in Paul's laboratory. I soon learned that Paul was from Kiskunhalas and that he had been in a concentration camp in Germany because he was Jewish. Despite this experience, Paul was not a bitter person. In fact, he loved life, had a delightful sense of humor, and was a very compassionate person. As a mentor, Paul was patient, challenging, and rigorous in experimental design and research methods. He provided continued support to his students and he also became a good friend to many of us.

Paul contributed to our understanding of the field of lipoprotein metabolism in many ways. We briefly highlight some of his many contributions in the area of apolipoprotein metabolism below.

When Paul began his career in lipoprotein metabolism, much of the work in this area had centered on intestinal absorption of dietary fats (1) and there was interest in the hepatic secretion of lipoproteins (2–4). Paul set out to determine whether the liver secreted proteins together with lipids in the form of lipoproteins by using liver perfusions of animals fed chow or cholesterol-enriched diets. He showed that the liver secreted proteins into VLDL, LDL, HDL, and a "lipoprotein-free" [density > 1.21 g/ml] fraction (5, 6). This protein fraction did not have a core of neutral lipids and thus had a very high density. The lipoprotein-free fraction was intriguing because some of its protein components "shuttled" between the lipoprotein-rich and lipoprotein-free fraction, depending on the metabolic state of the animal. When Paul administered orotic acid to chow-fed or cholesterol-fed rats, there was a deficiency of plasma VLDL and LDL, and a reduced secretion of HDL and the lipoprotein-free fraction. However, clofibrate prevented orotic acid induced-fatty liver and the changes in HDL and the lipoprotein-free fraction (7–11). In contrast, allylisopropylacetamide induced fatty liver and hyperlipidemia, including increases in HDL (12).

In subsequent years, the saga of lipoprotein metabolism became more complex with the identification of various apolipoproteins and of lipoprotein subclasses. The apolipoproteins came to the forefront of research in the 1970s. Paul's laboratory could now focus better on the characterization of the lipoprotein-free plasma fraction. First, however, he turned to the demanding task of purification of apolipoproteins, antibody production, and the establishment of immunoassays for apolipoprotein (apo) B, apoAs, apoE, and apoCs. These reagents were not available commercially at the time. Although most of the major apolipoproteins were studied in Paul's laboratory, he focused on apoA-IV because it was one likely candidate for the protein that moved bi-directionally between the lipoproteins and the lipoprotein-free fraction in plasma.

ApoA-IV was originally isolated in rat plasma HDL by Paul's colleague, John Swaney, Ph.D., a biochemist in the research group at Einstein (13). Paul's group showed that apoA-IV is a constituent of VLDL, HDL, and the lipoprotein-free plasma fraction (14, 15). He also showed that the apolipoprotein is synthesized by the intestine along with apoB and apoA-I, and its synthesis is highly inducible by fat absorption (16). In several studies, his group noted that apoA-IV was persistently present in the lipoprotein-free fraction in plasma and the amount varied depending on the metabolic status (17, 18). ApoA-IV could move bi-directionally between the lipoprotein-free plasma fraction and an HDL subclass in the presence of LCAT (19–21). Moreover, apoA-IV also could mediate "reverse cholesterol transport" in vitro (22). The model that emerged from these studies was that apoA-IV is secreted by the intestine in response to fat absorption and was a constituent of lymph chylomicrons and HDL; in plasma, the apolipoprotein associated principally with HDL and was also a "free apolipoprotein" as a result of lipolysis. In turn, apoA-IV could reassociate with a subclass of HDL through the action of LCAT.

If apoA-IV could have a bi-directional mobility between lipoproteins and lipoprotein-free plasma, could this apolipoprotein also move into the interstitial fluid and serve a function in reverse cholesterol transport? To address this question, Paul's laboratory decided first to characterize lipoproteins in the peripheral lymph in dogs (23–26). The group found that in normocholesterolemic and hypercholesterolemic dogs, prenodal lymph lipoproteins resembled their plasma counterparts; the smaller lipoproteins were present in higher concentrations than the larger; lymph HDL varied in size and a large fraction had a discoidal shape stacked in rouleau structures, particularly in diet-induced hypercholesterolemia. However, free cholesterol content of the lymph lipoproteins was higher than in the plasma counterparts. Of interest, lymph HDL also was enriched in apoA-IV compared with its counterpart in plasma (23–26).

The studies in dog peripheral lymph provided an opportunity to examine in vivo the two HDL subclasses that played a significant role in the transport of cholesterol from peripheral tissues to the liver. Both HDLs had a disk-like shape but one had apoA-IV and apoE and the other HDL had apoA-I as the main constituent. Paul's team proposed that discoidal HDLs were acceptors of free cholesterol from peripheral tissues and that they were vehicles that shuttle between the extravascular and intravascular spaces facilitating cholesterol transport between the two compartments. They proposed further that the HDL apoA-IV/E fraction would deliver cholesterol to the liver directly through a receptor-mediated pathway while the apoA-IV would dissociate and shuttle back to the extravascular space to repeat the cycle. Both HDL A-IV/E and HDL A-I became spherical through LCAT reaction (23). In this scheme, apoA-IV seemed to be the protein that shuttled bi-directionally between lipoprotein-rich and lipoprotein-free plasma fraction. ApoA-I also seemed to have a similar role. Paul's group next turned their attention to translational clinical research in HDL.

The quest for clinical significance of disk-like HDLs (27) led Paul's laboratory to develop additional methods that would simplify population studies. Using a quantitative and stringent 2-D method that separates HDL fractions by net surface charge and size, they showed that: *1)* the

free Apo A-I like particles were present in human plasma (28); *2*) there are 12 HDL particles; *3*) Apo A-I is the main apolipoprotein constituent of the particles associated with high HDL cholesterol and these are deficient in subjects with insulin resistance and/or coronary heart disease (29, 30); and *4*) abnormalities in the HDL subclass distribution were reversed by statin therapy (31, 32). Clearly, HDL is more complex than LDL but the suggestion from the statin studies was that reductions in LDL (and its precursors) impacted HDL speciation.

Nota bene

We wish the Roheim family well. We also share the concern expressed on October 17, 2008, by Paul's very young and wise grandson, who asked, "how can I make a difference in life?" Perhaps this memorial provides insight into how his grandfather made a significant difference in many lives.

The faculty of the Department of Physiology of the LSU Health Sciences Center has established the Paul S. Roheim, M.D. Excellence in Research Award. It will be bestowed on a graduate student who demonstrates excellence in scientific research. Contributions may be sent to: LSUHSC, Department of Physiology, 1901 Perdido Street, Room 7205, New Orleans, LA 70112; attn: Leslie A. Brennan, MHSA. Checks can be made payable to: LSU Health Science Center Foundation–Reference # 622015.

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