The Fats of Life

Inside This Issue…

To ***Join the Division***, go to http://www.aacc.org/AACC/members/divisions/lipids/ and click the Join Division link (you'll need to log in to AACC's website).

Have Questions about lipoproteins and vascular disease-related topics? If so, join the Division Listserv: https://my.binhost.com/lists/listinfo/aacc-lipo-vasc-div

Daniel M Hoefner produced this issue of *The Fats of Life*.

What is the connection between McAllen, Texas and our Lipoproteins and Vascular Diseases Division? That is a relevant story for this issue of *FATS*.

McAllen is a Texas border town with the lowest per capita income in the US, but one of the highest per capita Medicare costs. Their income averages $12,000, compared to average Medicare costs of $15,000, which means that each eligible person consumes more than their total income in health care costs. And of course the Federal Government or rather we as taxpayers make up the difference! This unfortunate story is detailed in a highly interesting article by Atul Gawande in *The New Yorker* issue of June 1, 2009*. The author, in the typical thoughtful and lucid *New Yorker* style, contrasts McAllen with other communities with much lower health care costs, even as low as one third of those in McAllen such as Rochester MN, home of the Mayo Clinic, Marshfield WI with their well known clinic, and Boise ID. And, by various indices, overall quality of care is actually better in the lower cost communities; evidence suggests there is little relationship between quality of health care and cost.

According to the author, the primary difference affecting medical costs is neither the quality of care nor the burden added by excessive and defensive medicine to avoid malpractice claims, but rather in the intent of the medical providers. In McAllen, the primary focus has evolved to be more on the business aspects, using medical services to drive revenue with the care entities viewed as profit centers. By contrast, in the lower cost areas, the focus tends to be more on the service aspects of medical care. Providers in areas with lower costs tend to take a more integrated and preventive approach, including focusing on the overall needs of the patient rather than simply treating and billing.

We are all aware that delivery of healthcare and the associated economics are again much in the news and a stated priority of the current US administration. And it is about time. Per capita healthcare costs in the US are more than double those of the next highest county, Switzerland, and currently consume about 17% of the GDP. At the current rate of increase and in the absence of major intervention, runaway costs will bankrupt the country in our lifetimes. And this problem is not limited to the US. Increasing medical costs follow chronic conditions such as the cardiovascular diseases and their precursors; smoking, obesity, metabolic syndrome and diabetes, which are spreading with the western lifestyle throughout the world. The World Health Organization predicts by next year cardiovascular diseases will become the major cause of morbidity and mortality worldwide.

Among many other changes, fixing health care must shift attention from the current focus on treatment, with often expensive interventions, to prevention of diseases. A more prevention-oriented system will help in controlling exploding medical costs. And, speaking of prevention, this brings us to the Lipoproteins and Vascular Diseases Division, which this year celebrates 20 years as a permanent division following the first 3 years as a provisional division of AACC. "Old timers" will remember the division had its genesis in the aftermath of the Lipid Research Clinics program. The LRC Coronary Primary Prevention Trial, funded by NIH through the Lipid Research Clinic's Program, reported in 1984, was the first major placebo controlled study to demonstrate that lowering cholesterol could reduce CVD events. This study lead to the NIH sponsored National Cholesterol Education Program and the consensus based Adult Treatment Panel guidelines for managing patients at risk, first released in 1988. Mevacor, or lovastatin, the first commercially successful statin drug, came into use in the US in 1987 and lead to the succession of increasingly effective statins, which have contributed to declining CVD event rates. These developments provided the evidence and the tools to enable a shift from treating the consequences of CVD to preventing the development of the underlying atherosclerosis. However, this changing focus has already consumed two

*http://www.newyorker.com/reporting/2009/06/01/090601fa_fact_gawande

decades and must progress even further to reduce the burden of cardiovascular diseases in the US and other countries throughout the world.

That exciting period in the mid to late 1980s was a major turning point in the move towards prevention. And the LVDD has been a major contributor from the beginning. LVDD members have lead efforts to improve and standardize the lipid/lipoprotein assays, making test results more uniform and reliable. Members have contributed many important technical papers to the literature and organized various presentations to lab and physiccian groups. The Division has also sponsored educational programs such as the early Manufacturer's Workshops and the current International Standardization Programs. Informative books have been published through individual and collective efforts such as the *Handbook of Lipoprotein Testing*.

Now, hopefully, we are at another turning point in the practice of medicine. We in the LVDD can proudly claim that we have been on the right side of history already for over two decades as our focus from the beginning has been driving and supporting preventive efforts. As we move forward into this new era in medical practice our support will continue to be crucial. We will of course still provide reliable lab values, which are the basis for characterizing, treating and monitoring patients. We will continue to develop more definitive and cost effective assays for better identifying patients at risk. And we will need to continue educating practitioners in the nuances of emerging technologies.

Those still active in the Division 20 years hence may look back with even greater satisfaction, having assisted in conquering cardiovascular diseases and thereby contributing to a relative decline in health care costs. That is provided we all as professionals and as citizens make the appropriate decisions now. And McAllen, TX may look forward to a day when their residents spend only a fraction of their total income on health care.

Russ Warnick, Editor
The Fats of Life

The Summer issue of the *FOL* is always associated with the Annual AACC meeting, which will take place in Chicago this year. In addition to the usual executive meeting on Sunday, LVDD again has two major evening events. On Monday night, the traditional award ceremony and celebration of the 20th anniversary of LVDD will be followed by two high-quality presentations. On Tuesday night, two other high-quality presentations will discuss current issues in cardiovascular research and testing. A detailed description of these events has already appeared in the Chair's Corner section of the Spring issue of the *FOL* and is retrievable from AACC-LVDD's website, so the following is just a brief summary for time and location:

LVDD Executive Committee (Board) Meeting

(Since this also serves as a division business meeting, no registration is required and all members are invited and welcome!)

Sunday, July 19 8:00am – 11:00am
Hyatt Regency Chicago Hotel (Columbian Rm)

Annual LVDD Dinner Meeting

Current Topics in Cardiovascular Disease

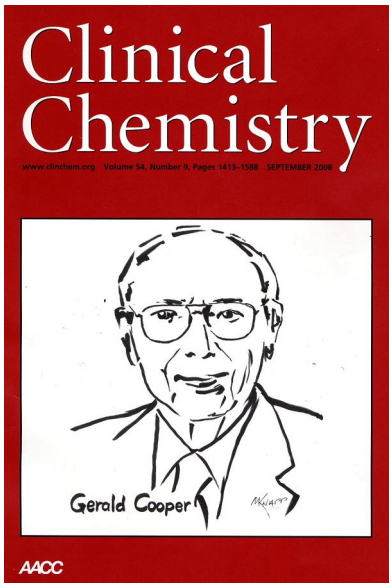
Monday, July 20 - 5:30pm – 9:30pm
Hyatt Regency Chicago Hotel (Columbus Hall A, B, C, D)

International Lipoprotein Standardization Forum

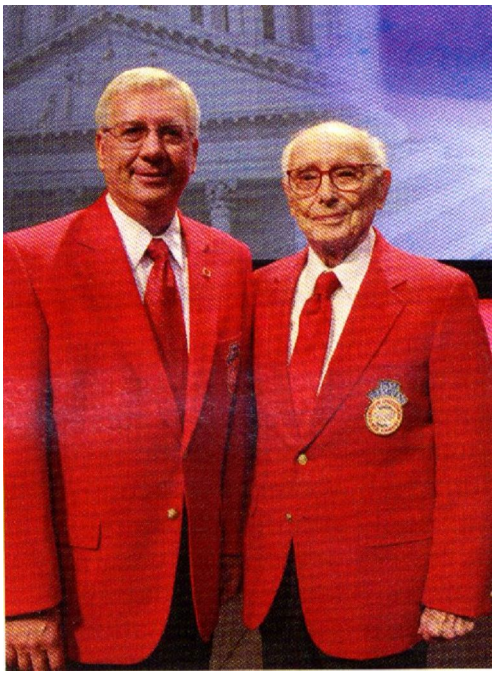
Tuesday, July 21 - 6:00pm – 9:30pm
Hyatt Regency Chicago Hotel (Columbus Hall K, L)

Although it may be difficult, if not impossible, to define the precise time for the foundation of our division (it took a few years from the original thought to formalize the division at AACC), we decided to celebrate our 20th anniversary this year. Our first Chair (G. Russell Warnick) was elected in 1989 and this justifies the anniversary in 2009. Regretfully, one of our founding members is no longer able to participate in this celebration. The sad news is Gerald R. Cooper, MD, PhD, often referred to as the "Father of Cholesterol," has passed away on May 25, 2009. Dr. Cooper published in the first volume of *Clinical Chemistry* in 1955 and was one of the Past Presidents of AACC. Working at CDC in Atlanta, GA, he spent over 50 years improving the accuracy and precision of serum lipid testing. He was a major force behind the Cholesterol Standardization Program and he continued to have a productive life by actively working in this area almost until his death at the age of 94 years (see his recent publication list, below)—his last publication appeared just three months before his death this year. LVDD honored Dr. Cooper's extensive contributions to the improved diagnosis of cardiovascular diseases by establishing the Cooper Award in 1992. This award is given every other year for outstanding contributions to service in the area of lipoproteins and vascular diseases and Dr. Cooper was the first recipient of it.

Dr. Cooper's life, career, work ethic, and resolute optimism have been described in detail in an "Inspiring Minds" article by Misia Landau in the 2008 September issue of *Clinical Chemistry* (Landau M. "Gerald Cooper." Clin Chem. 2008 Sep;54(9): 1578-9). As shown below, this issue also carried a sketch of Dr. Cooper on its cover. Obituaries have already appeared about Dr. Cooper in the AACC *eNewsletter* and the July issue of *Clinical Laboratory News* (CLN), and an obituary is planned for publication in *Clinical Chemistry*, as well. A photograph taken just about a year ago during the 2009 Annual AACC meeting in Washington, DC shows the Dr. Cooper full of life and energy, as we knew him (see below). In this photo, he is accompanied by his colleague and friend, Gary



Myers, PhD, from CDC, who himself is another Past President of AACC.



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Clin. Lab. News 2009,35(7):18
Photo: Oscar Enzig Photography

Dr. Cooper's publications from the last decade include the following:

1. NACB LMPG Committee Members, Myers GL, Christenson RH, Cushman M, Ballantyne CM, **Cooper GR**, Pfeiffer CM, Grundy SM, Labarthe DR, Levy D, Rifai N, Wilson PW. National Academy of Clinical Biochemistry Laboratory Medicine Practice guidelines: emerging biomarkers for primary prevention of cardiovascular disease. Clin Chem. 2009 Feb;55(2):378-84. Epub 2008 Dec 23.

2. McNamara JR, Warnick GR, **Cooper GR**. A brief history of lipid and lipoprotein measurements and their contribution to clinical chemistry. Clin Chim Acta. 2006 Jul 23;369(2):158-67. Epub 2006 Mar 24.

3. Kimberly MM, **Cooper GR**, Myers GL. An overview of inflammatory markers in type 2 diabetes from the perspective of the clinical chemist. Diabetes Technol Ther. 2006 Feb;8(1):37-44.

4. Myers GL, Rifai N, Tracy RP, Roberts WL, Alexander RW, Biasucci LM, Catravas JD, Cole TG, **Cooper GR**, Khan BV, Kimberly MM, Stein EA, Taubert KA, Warnick GR, Waymack PP; CDC; AHA. CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: report from the laboratory science discussion group. Circulation. 2004 Dec 21;110(25):e545-9.

5. Rifai N, **Cooper GR**, Brown WV, Friedewald W, Havel RJ, Myers GL, Warnick GR. Clinical Chemistry journal has contributed to progress in lipid and lipoprotein testing for fifty years. Clin Chem. 2004 Oct;50(10):1861-70. Epub 2004 Aug 12.

6. Kimberly MM, Vesper HW, Caudill SP, **Cooper GR**, Rifai N, Dati F, Myers GL. Standardization of immunoassays for measurement of high-sensitivity C-reactive protein. Phase I: evaluation of secondary reference materials. Clin Chem. 2003 Apr;49(4):611-6.

7. Blanck HM, Bowman BA, **Cooper GR**, Myers GL, Miller DT. Laboratory issues: use of nutritional biomarkers. J Nutr. 2003 Mar;133 Suppl 3:888S-894S.

8. **Cooper GR**, Myers GL, Kimberly MM, Waymack AP. The effects of errors in lipid measurement and assessment. Curr Cardiol Rep. 2002 Nov;4(6):501-7.

9. Warnick GR, Myers GL, **Cooper GR**, Rifai N. Impact of the third cholesterol report from the adult treatment panel of the national cholesterol education program on the clinical laboratory. Clin Chem. 2002 Jan;48(1):11-7.

10. Myers GL, Kimberly MM, Waymack PP, Smith SJ, **Cooper GR**, Sampson EJ. A reference method laboratory network for cholesterol: a model for standardization and improvement of clinical laboratory measurements. Clin Chem. 2000 Nov;46(11):1762-72.

11. Caudill SP, **Cooper GR**, Smith SJ, Myers GL. Assessment of current National Cholesterol Education Program guidelines for total cholesterol triglyceride, HDL-cholesterol, and LDL-cholesterol measurements. Clin Chem. 1998 Aug; 44(8 Pt 1):1650-8.

12. Caudill SP, Smith SJ, **Cooper GR**, Myers GL. Adequacy of NCEP recommendations for total cholesterol, triglycerides, HDLC, and LDLC measurements. Clin Chem. 1998 May;44(5):1063-6.

I look forward to seeing you at the AACC meeting in Chicago.

Sincerely,

Gyorgy (George) Csako, MD
Chair, LVDD, AACC

FATS OF LIFE

The Newsletter of the AACC Lipids and Lipoprotein Division

Volume I No. 1 June 1987

San Francisco AACC Highlights

WORKSHOPS

Tuesday, July 21 -- 224
Apolipoproteins and Coronary Heart Disease - Clinical Relevance, Methods of Assay and Role of Genetics
Presented by BA Kottke and W Patsch

ROUNDTABLES

Monday, July 20
405 Laboratory Testing in Lipid Disorders:
505 Clinical Prespective

412 Fetal Lung Maturity Testing - Critical
512 Assessment of Laboratory Approaches

Tuesday, July 21
452 The Enzymatic Determination of
552 Lecithin, Sphingomyelin and PG

460 Laboratory Testing in Lipid Disorders:
560 Standardization Problems

SELECTED TOPICS

Monday, July 20
Session I - Apolipoproteins: Biochemistry, Metabolism, and Clinical Significance
Presentations by Thomas Innearity, Ph.D., Ernst J. Schaefer, M.D., Gerald Cooper, M.D.,Ph.D. and Herbert K. Naito, Ph.D.

Leaders of the L&LD

G. Russell Warnick, M.S. -- Chairman of the L&L Division --

received his M.S. in biochemistry from Utah State University in 1970. Russ served his country as a Captain in the Medical Service Corps with the U.S. Army and with his background in biochemistry was assigned duty with an Army Referral Laboratory where his interest for clinical chemistry was awakened. He joined the Northwest Lipid Research Clinic Laboratory in 1973 and worked with John Albers, Ph.D. and became involved with lipids and lipoproteins. Currently, Russ is Director of the Lipoprotein Laboratory. Recently, Russ received a MBA from City University, Seattle, WA. in 1982. On a personal note, Russ is a proud father of five children, ages 10 - 18 yo, enjoys outdoor activities such as back packing, sking, running, and squbba diving. Russ ran a marathon at the age of 42 and noone would have guessed Russ is even close to that age.

Donald A. Wiebe, Ph.D. -- Secretary of the L&L Division --

received his degree from the University of Iowa, Iowa City, IA. in organic chemistry in 1973. During 1972, he joined the Iowa Lipid Research Clinic as Laboratory Director.

(Continued on page 2)

L&L D Leaders Continued

Don quickly discovered that the organic chemistry he studied had very little to do with lipids and lipoproteins. During 6 years with the LRC, he became interested in clinical chemistry. Between 1978-80 he completed a 2-year post-doctoral fellowship at Iowa in clinical chemistry. In 1980, he joined the staff at the Centers for Disease Control and spent four years with the likes of Gerald Cooper, Gary Myers, Eric Sampson and Adrian Hainline. CDC is a marvelous place to work but an opportunity to become a faculty member at the University of Wisconsin transferred him to Madison. Currently, Don is Associate Director of Clinical Chemistry and Director of the Toxicology Laboratory.

Joseph D. Artiss, Ph.D. -- Treasurer of the L&L Division --

received his Ph.D. in 1980 from the University of Windsor, Ontario in clinical chemistry under the direction of R.J. Thibert and Bennie Zak. Its not too difficult to understand where Joe's interest in lipids and lipoproteins came from with these two advisors. Following his doctoral training, Joe accepted a position as clinical chemist at St. Joseph's Hospital (his name sake) and lectured in biochemistry at University of Western Ontario, London, Ontario. He is currently Associate Division Head of Chemistry at Detroit Receiving Hospital/University Health Center, Detroit, MI. and is soon to be promoted to Associate Professor in Pathology at Wayne State University. His research interests includes enzymic reactions, especially as they are coupled to peroxidase for detection. As a point of interest, Joe must cross an international border to and from work each day. Joe assures us there is no tax advantage, just a favorable exchange rate.

Herbert K. Naito, Ph.D. -- Member-at-Large of the L&LD --

received his degree in physiology at Iowa State University, Ames, IA. and followed this with a two year post-doctoral program in experimental pathology at the Cleveland Clinic. Herb has held various appointments during his 16 years at the Cleveland Clinic Foundation. Herb is Head of the Lipid Section. His interest and contributions in the field of lipids and lipoproteins is easy to understand since Lena Lewis was his mentor for a number of these years. Recently, Herb accepted the task of spearheading the National Cholesterol Education Program efforts in collaboration with NHLBI, NCCLS, AACC, CDC, CAP and other agencies. Thus, his recent focus has been on cholesterol standardization issues.

ATTEND THE L&LD GENERAL MEETING AND MIXER

MONDAY, JULY 20th

Hotel Meridien

in the Cabernet I Room

TIME: 5:00 - 7:00 pm

There will be a short business meeting followed by pleasant conversation with various members of our division -- an excellent opportunity to meet some facinating people in the L&LD.

Bring a friend & join the fun.

Incourage others to join your Lipids and Lipoproteins Division

APOLIPOPROTEINS -- WHAT'S HAPPENING?

Editor's comment--

I asked Dr. Cooper to submit a short narative to discribe to our members the efforts of the IUIS/NHLBI/CDC collaborative studies for apoprotein standardization. The following response was promptly received from Gerry, thank you.

An apolipoprotein (Apo) A-I and B serum reference material (RM) has been developed, characterized and assigned consensus reference values in a cooperative project sponsored by the International Union of Immunological Societies (IUIS), the National Heart, Lung and Blood Institute (NHLBI) and the Centers for Disease Control (CDC). Collaborative studies on this IUIS Apo A-I and B reference material by 55 participating laboratories found a total CV of about 20% for Apo A-I and 30% for Apo B, of which 75 - 95% was among-laboratory error. Use of this IUIS reference material, along with improvement of methodology in the collaborating laboratories in 1986, revealed about a 60% improvement in among-laboratory error. Collaborative studies on this IUIS-Apo RM are continuing with manufacturers of Apo diagnostic products and laboratories conducting methodology research.

It should be obvious to anyone who has viewed recent advertisements for some of the new apolipoprotein products been offered by several manufacturers as to the impact this reference material is having on their products. The user is going to benifit from all this hard work and I know that Dr. Cooper has played a significant role.

You are invited to submit articles for this Newsletter -- this forum is for sharing information among the L&LD members and your articles will be welcomed by all -- if you don't mind a 'little' editing now and then -- THANK YOU.

Lipids and Lipoprotein Division sponsors the following Conference in San Francisco

Issues of Lipid Standardization and Reference Materials
Sunday, July 19 from 1:00 - 5:00 pm
Ramada Renaissance -- Da Vinci I

1:00 - 1:05 INTRODUCTION

1:05 - 1:25 Herbert Naito, Ph.D.
National Cholesterol Education Program

1:25 - 1:35 Raymond Vanderlinde, Ph.D.
National Reference System - Cholesterol

1:35 - 1:55 Gary Myers, Ph.D.
Centers for Disease Control

1:55 - 2:15 Russell Warnick, M.S.
Reference Materials Criteria

2:15 - 2:35 Al Hartmann, M.D.
College of American Pathologists

2:35 - 2:50 One and Only Break

2:50 - 3:10 Beckman Instruments, Inc.
Nathan Gochman, Ph.D.

3:10 - 3:30 DuPont Company
Wendell O'Neal, Ph.D.

3:30 - 3:50 Technicon Corporation
Jack Levine and Janet Carrubba

3:50 - 4:10 American Dade
Robert Bodden

4:10 - 4:30 Eastman Kodak Company
Neil Greenberg, Ph.D.

4:30 - 5:00 General Discussion & Closing Comments

CONTRIBUTIONS

L&LD received contributions from the following companies and we thank them for their valuable support of our Division.

Eastman Kodak Company
Beckman Instruments, Inc.
E.I. du Pont De Nemours & Co.
Diagnostic Chemicals Ltd.
Boerhringer Mannheim Diag.

Their contributions will provide the funds to support the various Division events at San Francisco.

MEMBERSHIP

L&LD is part way through its first year and already the membership has reached an outstanding 206. Almost 1/4 of our members come from outside the U.S. (48) which is really appreciated. We will publish and circulate a list of Divsion members, possibly this Fall.

Thank You

The following companies provided funds that supported our first meeting and hospitality room during the Chicago AACC meeting:

Eastman Kodak Company
Boerhringer Mannheim Diag.

Their support was much appreciated and if you meet a representative from one of these firms, please let them know how much you appreciate their contribution.

How Can Your Company Help?

Its easy, just contact our treasurer, Dr. Joseph Artiss at the following address or call and talk to him.

Joseph D. Artiss, Ph.D.
Depart. of Pathology
Wayne State Sch. of Med.
Wayne State University
Detroit, MI 48201
(313) 577-1140

What should be the name of our newsletter - Fats of Life ??

Send your thoughts, comments, sugesstions or ideas to one of the team members - or bring them to our meeting and social hour in San Francisco - Monday 5 - 7pm - Hotel Meridien.

Helpful Lab Hints

Our newsletter might be an excellent tool to share ideas with your fellow members that work with lipids and lipoproteins on a daily basis.

SUGGESTIONS

1. Using the new Beckman tabletop ultracentrifuge to fractionate serum or plasma lipoproteins.
2. What new instruments are being used to measure chol, trigs, or other lipids?
3. New reagent systems - such as the BMD glycerol oxidase method for trigs.
4. New electrophoresis methods.
5. Extraction techniques for lipids.
6. Suggestions or concerns with the new apolipoprotein methods that are available.
7. Any suitable topic can be addressed.

Do You Want To Take An Active Role in L&LD??

Simple, let one of the division team members know of your interest. There are numerous ways to get involved --

1. Become a team member (elections will take place next year for new officers)
2. Join a committee for this newsletter? -- join the Publication Committee
3. Join the Program Com. - assist with a workshop, selected topic, round-table or other Division sponsored event at a National AACC meeting?
4. Possibly, you want to serve as a Reveiwer of lipid articles for Clinical Chemistry - we can share this information with the editor.
5. How about joining the Membership- Finance Committee.
6. There is always the Research Initiatives Committee.
7. Or many other ways...

ABC's of Cholesterol Testing and Standardization

This new pamphlet written by Herb Naito, Ph.D. and Al Hartmann, M.D. will be available at the AACC Mtg.

Stop by the CAP Booth

We have asked the question -- how can you help the L&LD?

It is fair for you to ask -- how can L&LD assist me?

Let us hear from you!!!

Who to blame for this newsletter?

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Madison, WI 53792

Manfredi Rizzo‡ and Kaspar Berneis*
‡Department of Internal Medicine and Emerging Diseases, University of Palermo, Italy;
***Clinic for Endocrinology, Diabetes & Clinical Nutrition, University Hospital Zurich, Switzerland.**
Correspondence to: Manfredi Rizzo, MD, PhD; Dipartimento di Medicina Clinica e delle Patologie Emergenti; Universita' di Palermo; Via del Vespro, 141; 90127 - Palermo - Italy
Ph. and Fax: +39 (091) 655-2945; E-mail: mrizzo@unipa.it

Introduction

Higher plasma triglycerides levels and decreased high density lipoproteins (HDL)-cholesterol concentrations are usually accompanied by the presence of small, dense low density lipoproteins (LDL) in the "atherogenic lipoprotein phenotype" (ALP): this phenotype is highly atherogenic and its prevalence may suggest higher overall burden of atherosclerotic disease than that associated with hypercholesterolemia [1,2]. The atherogenic dyslipidemia is associated to abdominal obesity and insulin resistance [3,4] and represents one of the components of the metabolic syndrome [5,6]. It has been also suggested that the clinical importance of ALP probably exceeds that of LDL-cholesterol, because many more patients with coronary artery disease are found to have this trait than hypercholesterolemia [7,8].

As stated by the National Cholesterol Education Program Adult Treatment Panel III [9], there is evidence that each component of the atherogenic lipoprotein phenotype is individually atherogenic, but the relative contribution of each component cannot be easily determined. Therefore, it has been suggested to consider this trait as a whole as a "risk factor." This is supported by data from epidemiological studies considering high-risk populations, which showed that the contribution to cardiovascular risk of each individual component cannot be dissected from the sum of all factors [10,11].

Also, increasing evidence suggests that the *quality* rather than only the *quantity* of LDL exerts a great influence on cardiovascular risk [1]. In fact, LDL particles do not comprise a homogenous population, but multiple subclasses with discrete size and density, different physicochemical composition, metabolic behavior and atherogenicity, with at least four major subspecies: large LDL-I, medium LDL-II, small LDL-III, very small LDL-IV [12] (Figure 1). Based on measurement of peak particle diameter or ultracentrifugal density, individuals generally cluster into two broad subgroups, the majority with a predominance of larger or medium sized LDL (pattern A) and a substantial minority with a higher proportion of smaller, more dense LDL particles (pattern B) [12]. The predominance of small, dense LDL, which seems to be associated with an approximately three-fold increased risk for coronary heart disease (CHD) [1], has been accepted as an emerging cardiovascular risk factor by the National Cholesterol Education Program Adult Treatment Panel III [9].

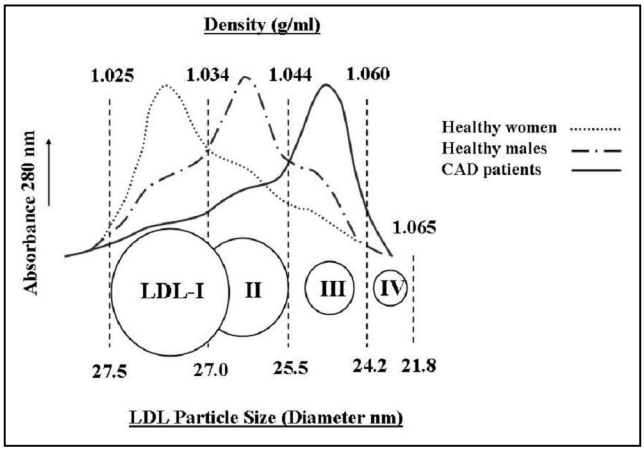

Figure 1: LDL subclass distribution according to size and density (as modified from 61). CAD: coronary artery disease.

The clinical significance of small, dense LDL

To date, the association of LDL size with cardiovascular diseases has been tested in over 50 studies, including cross-sectional and prospective epidemiologic as well as clinical intervention trials [1]. The vast majority of these studies showed a strong and significant association of small, dense LDL with increased coronary artery disease (CAD) risk at univariate analyses. Yet, since LDL size is rarely a significant and independent predictor of CAD risk after multivariate adjustments for confounding variables (including plasma triglycerides

levels and HDL-cholesterol concentrations), it is still on debate if the increased atherogenic potential of small, dense LDL may be a consequence of the broader pathophysiology of which these particles are a part [13-16].

Several reasons have been suggested for the atherogenicity of small, dense LDL. In relation to larger, more buoyant LDL: small dense LDL are taken up more easily by arterial tissue, have decreased sialic acid content and receptor-mediated uptake, as well as increased oxidative susceptibility and reduced antioxidant concentrations [17]. Therefore, screening for the presence of small, dense LDL may potentially identify subjects with higher vascular risk and may contribute in directing specific interventions of cardiovascular prevention. Increased levels of atherogenic small, dense LDL are a feature of subjects at very-high cardiovascular risk, such as those with CAD and type-2 diabetes [18,19]. Yet, recent studies have shown that other categories of subjects at high cardiovascular risk may show higher levels of these particles. Some authors recently studied subjects with clinical forms of non-coronary atherosclerosis, including carotid artery disease, peripheral arterial disease and abdominal aortic aneurysm, i.e., subjects that carry a risk for CAD equal to those with established CAD [9].

Landray *et al*. in 1998 [20] reported an association between small, dense LDL and asymptomatic carotid atherosclerosis and this has been confirmed by other similar studies in healthy individuals [21-23]. Other authors found a significant relationship between LDL size and the occurrence of preclinical and clinical carotid atherosclerosis [24-26]. In a clinical trial, Van Tits *et al*. [27] have shown an association between baseline LDL size and intima media thickness regression by statin therapy (with atorvastatin and simvastatin) and this has been confirmed in another study by Wallenfeldt *et al*. [28]. We have recently found that patients with abdominal aortic aneurysm have a smaller LDL size due to increased levels of small, dense LDL [29], a finding that was also present in subjects with peripheral arterial disease [30], which is in line with previous data by O'Neal *et al*. [31].

In other recent studies, elevated levels of small, dense LDL were found in patients with different metabolic diseases, including polycystic ovary syndrome and growth hormone deficiency [32,33], as well as in women with gestational diabetes [34]; notably, in most of them, the predominance of small, dense LDL characterized their type of dyslipidemia, alone or in combination with elevated triglycerides and reduced HDL-cholesterol concentrations. Evidence also suggests that small, dense LDL are independently associated with the metabolic syndrome. Already in 1995, Haffner *et al*. reported that LDL size was decreased in subjects with multiple metabolic disorders [35]. In a recent study, we have extended such observations, showing a clear significant association between LDL peak particle size and number of components of the metabolic syndrome, as assessed by the joint American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. The importance of LDL particle size as an early marker of dyslipidemia and insulin resistance is further highlighted by the intriguing finding that in school-age children central adiposity was associated with smaller LDL particle size [36].

Recent studies [37-40] further suggested that small, dense LDL may represent a valuable marker for diagnosis and severity of the metabolic syndrome. Using the *Lipoprint* system, Gazi *et al*. [38] have shown that subjects with the metabolic syndrome exhibit significantly higher concentrations of small, dense LDL than individuals who do not fulfill the criteria for such a syndrome. Using a different methodology, we recently confirmed that small, dense LDL are reduced in the metabolic syndrome and further showed an independent predictive role for future cardio- and cerebrovascular events [41].

The clinical impact of the modulation of small, dense LDL

Weight reduction and increased physical activity may constitute first-line therapy; in addition, hypolipidemic agents are able to favorably alter LDL size and subclasses [42]. Particularly, medications with triglycerides-lowering effects shift LDL peak size from smaller, more dense to larger, more buoyant particles; in fact, reduced availability of

triglycerides-rich particles lead to reduced production of small dense LDL. This has been shown for fibrates and niacin: these substances lower preferentially small dense LDL [43]. Statins potentially lower large, medium and small LDL particles, but a strong variation has been noticed among the different agents. Pravastatin and simvastatin showed a limited net effect on LDL subclasses, while treatment with fluvastatin and atorvastatin resulted more frequently in a beneficial effect; promising data were also recently reported by the use of rosuvastatin (reviewed in [44,45].

Other studies have more interestingly investigated if the therapeutic modification of LDL size may be significantly associated with reduced cardiovascular risk. Such investigations used arteriographic changes as outcome variables and have reported that benefit was concentrated in patients with a predominance of small, dense LDL who received treatment that tended to lower small dense LDL. These studies included the "Stanford Coronary Risk Intervention Project" (SCRIP), the "Familial Atherosclerosis Treatment Study" (FATS) and the "Pravastatin Limitation of Atherosclerosis in the Coronary Arteries" (PLAC-I) trial [46-48]. Lovastatin was administered in the SCRIP (with bile acid-binding resins, niacin or fibrates) and in the FATS (with colestipol, versus niacin and colestipol), pravastatin was used in the PLAC-I.

The therapeutic modulation of LDL size was significantly associated with reduced cardiovascular risk at univariate analysis. In addition, at multivariate analyses with adjustments for confounding factors, changes in LDL size by drug therapy were the best correlates of changes in coronary stenosis in FATS [48]. In PLAC-I, using logistic regression models that adjusted for lipid levels and other confounding factors, elevated levels of small LDL were associated with a nine-fold increased risk of CAD progression in the placebo group [46]. All these data seem to suggest that the therapeutic modification of LDL size may be significantly associated with reduced cardiovascular risk, even after multivariate adjustment for confounding factors. In addition, as already reported [49], although not directly demonstrated, the modulation of LDL size with fibrates probably contributed to the reduction of cardiovascular risk in two clinical trials, the "Helsinki Heart Study" and the "Veterans Affairs High-density Lipoprotein Cholesterol Intervention Trials Study Group" (VA-HIT) [50-52].

Yet, although fibrates are more powerful than statins in improving LDL quality, existing evidence suggest that statins are more powerful agents in reducing cardiovascular morbidity and mortality. Fenofibrate seems to be very effective in lowering small dense LDL, but the FIELD study [53,54] showed no significant reduction in primary end point in type-2 diabetics randomized to receive fenofibrate or placebo. In this study, triglycerides were reduced from 1.95 to 1.47 mmol/l; as it is expected that LDL distribution improves below the triglycerides threshold of 1.5 mmol/l, the findings of the FIELD study may argue against the concept that increasing LDL size is a major modulator of cardiovascular risk. In addition, in a subset statin-free cohort of the FIELD study, it was recently shown that fenofibrate produced a clear shift in HDL subspecies towards smaller more atherogenic particles [55].

Conclusions

Small, dense LDL are atherogenic particles. Yet, the small dense phenomenon applies to all lipoprotein particles, so that small dense chylomicron remnants, as well as small dense HDL may contribute to the atherogenic nature of the profile, but there is also evidence that large cholesterol-rich particles contribute to cardiovascular risk, such as large LDL particles [13]. This is further complicated by the fact that at the same level of LDL-cholesterol, higher-risk individuals with a predominance of small, dense LDL have significantly more particles than those with a predominance of larger, more buoyant LDL. The number of LDL particles in plasma is potentially important, because the arterial walls are exposed to these particles, and an increased number might increase atherogenicity independently of particle size.

Is higher risk of individuals with a predominance of small, dense LDL attributable to the fact that they have more LDL particles in total, or does the

smaller size contribute independently to CHD risk? Assessment of LDL size and subclasses does not provide information about the number of LDL particles, which has been usually estimated by measuring apoB concentrations, due to the presence of one apoB-100 molecule per LDL. Higher LDL particle concentrations seem to be very important in determining cardiovascular risk; however, few studies have assessed if the quantity rather than the quality of small, dense LDL may be stronger associated with that risk. In these studies, the number of total and smaller LDL particles has consistently been shown to be a significant and independent predictor of cardiovascular risk following multivariate adjustment for lipid variables.

In summary, such data underline the clinical importance of assessing LDL particle size and number in order to adequately establish cardiovascular risk. Since increasing evidence from prospective studies suggest the superiority of apoB or LDL particle number over traditional LDL-cholesterol measurement for the assessment of cardiovascular risk, different position statements have advocated in the last years a more routine measurement of apoB in clinical practice [56-59]. By contrast, the assessment of lipoprotein subclasses, such as small, dense LDL, should involve the use of well-established laboratory methods and this significantly limits its use in clinical practice; surrogate markers of small, dense LDL may be used in large clinical studies, but they should be interpreted with caution as they may give misleading results [60].

References

1) Rizzo M, Berneis K. Low-density-lipoproteins size and cardiovascular risk assessment QJM – Int J Med 2006; 99:1-14.

2) Austin MA, King MC, Vranizan KM and Krauss RM. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. Circulation 1990; 82: 495-506.

3) National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults - the evidence report. Obesity Res 1998;6(suppl 2):51S-209S

4) Carmena R. Type 2 diabetes, dyslipidemia, and vascular risk: rationale and evidence for correcting the lipid imbalance. Am Heart J 2005; 150:859–870.

5) Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005; 112:2735-52. 32.

6) Rizzo M, Berneis K. Small, dense low-density-lipoproteins and the metabolic syndrome. Diabetes/Metabolism Research and Reviews 2007; 23:14-20.

7) Sattar N, Petrie JR, Jaap AJ. The atherogenic lipoprotein phenotype and vascular endothelial dysfunction. Atherosclerosis 1998; 138: 229-35

8) Superko HR. Beyond LDL cholesterol reduction. Circulation 1996; 94: 2351-4.

9) National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106:3143-421.

10) Packard CJ. Small dense low-density lipoprotein and its role as an independent predictor of cardiovascular disease. Curr Opin Lipidol 2006; 17:412-7.

11) Gazi IF, Tsimihodimos V, Tselepis AD, Elisaf M, Mikhailidis DP. Clinical importance and therapeutic modulation of small dense low-density lipoprotein particles. Expert Opin Biol Ther 2007; 7:53-72.

12) Berneis KK, Krauss RM. Metabolic origins and clinical significance of LDL heterogeneity. J Lipid Res 2002; 43: 1363-1379.

13) Sacks FM, Campos H. Low-Density Lipoprotein Size and Cardiovascular Disease: A Reappraisal. J Clin Endocr Metab 2003;88:4525-32.

14) Lamarche B, Lemieux I, Despres JP. The small, dense LDL phenotype and the risk of coronary heart disease: epidemiology, patho-

physiology and therapeutic aspects. Diabetes Metab 1999; 25:199-211.
15) Lada AT, Rudel LL. Associations of low density lipoprotein particle composition with atherogenicity. Curr Opin Lipidol 2004; 15:19-24.
16) Cromwell WC, Otvos JD. Low-density lipoprotein particle number and risk for cardiovascular disease. Curr Atheroscler Rep 2004; 6:381-7.
17) Wierzbicki AS. Quality as well as quantity? Beyond low-density lipoprotein-cholesterol - the role of particle size. Int J Clin Pract 2007; 61:1780-2.
18) Lamarche B, Lemieux I, Després JP. The small, dense LDL phenotype and the risk of coronary heart disease: epidemiology, patho-physiology and therapeutic aspects. Diabetes Metab 1999;25: 199-211.
19) Krauss RM. Lipids and lipoproteins in patients with type 2 diabetes. Diabetes Care 2004; 27:1496-504.
20) Landray MJ, Sagar G, Muskin J, Murray S, Holder RL, Lip GYH. Association of atherogenic low-density lipoprotein subfractions with carotid atherosclerosis. Q J Med 1998;91:345-351.
21) Skoglund-Andersson C, Tang R, Bond MG, de Faire U, Hamsten A, Karpe F LDL particle size distribution is associated with carotid intima-media thickness in healthy 50-year-old men. Arterioscler Thromb Vasc Biol 1999;19:2422-30.
22) Bokemark L, Wikstrand J, Attvall S, Hulthe J, Wedel H, Fagerberg B. Insulin resistance and intima-media thickness in the carotid and femoral arteries of clinically healthy 58-year-old men. The Atherosclerosis and Insulin Resistance Study (AIR). J Intern Med 2001;249:59-67.
23) Hallman DM, Brown SA, Ballantyne CM, Sharrett AR, Boerwinkle E. Relationship between low-density lipoprotein subclasses and asymptomatic atherosclerosis in subjects from the Atherosclerosis Risk in Communities (ARIC) Study. Biomarkers 2004;9:190-202.
24) Liu ML, Ylitalo K, Nuotio I, Salonen R, Salonen JT, Taskinen MR. Association between carotid intima-media thickness and low-density lipoprotein size and susceptibility of low-density lipoprotein to oxidation in asymptomatic members of familial combined hyperlipidemia families. Stroke 2002;33:1255-60.
25) Watanabe T, Koba S, Kawamura M, Itokawa M, Idei T, Nakagawa Y, et al. Small dense low-density lipoprotein and carotid atherosclerosis in relation to vascular dementia. Metabolism 2004;53: 476-82.
26) Berneis K, Jeanneret C, Muser J, Felix B, Miserez AR. Low-density lipoprotein size and subclasses are markers of clinically apparent and non-apparent atherosclerosis in type 2 diabetes. Metabolism 2005;54:227-34.
27) van Tits LJ, Smilde TJ, van Wissen S, de Graaf J, Kastelein JJ, Stalenhoef AF. Effects of atorvastatin and simvastatin on low-density lipoprotein subfraction profile, low-density lipoprotein oxidizability, and antibodies to oxidized low-density lipoprotein in relation to carotid intima media thickness in familial hypercholesterolemia. J Investig Med 2004;52:177-84.
28) Wallenfeldt K, Bokemark L, Wikstrand J, Hulthe J, Fagerberg B. Apolipoprotein B/apolipoprotein A-I in relation to the metabolic syndrome and change in carotid artery intima-media thickness during 3 years in middle-aged men. Stroke 2004;35:2248-52.
29) Rizzo M, Krayenbühl PA, Pernice V, Frasheri A, Rini GB, Berneis K. LDL size and subclasses in patients with abdominal aortic aneurysm. Int J Card 2009; 134: 406-8.
30) Rizzo M, Pernice V, Frasheri A, Berneis K. Atherogenic lipoprotein phenotype and LDL size and subclasses in patients with peripheral arterial disease. Atherosclerosis 2008;197:237-241.
31) O'Neal DN, Lewicki J, Ansari MZ, Matthews PG, Best JD. Lipid levels and peripheral vascular disease in diabetic and non-diabetic subjects. Atherosclerosis 1998;136:1-8.
32) Berneis K, Rizzo M, Fruzzetti F, Lazzaroni V, Carmina E. Atherogenic lipoprotein phenotype and low-density lipoproteins size and subclasses in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2007;92:186-9.
33) Rizzo M, Trepp R, Berneis K, Christ ER. Atherogenic lipoprotein phenotype and LDL size and subclasses in patients with growth hormone deficiency before and after short-term replacement therapy. Eur J Endocr 2007;156:361-7.
34) Rizzo M, Berneis K. Altinova AE, Toruner FB, Akturk M, Ayvaz G et al. Atherogenic lipo-

protein phenotype and LDL size and subclasses in women with gestational diabetes. Diabetic Med 2008; 25:1406-11.
35) Haffner SM, Mykkanen L, Robbins D, Valdez R, Miettinen H, Howard BV, et al. A preponderance of small dense LDL is associated with specific insulin, proinsulin and the components of the insulin resistance syndrome in non-diabetic subjects. Diabetologia 1995;38:1328-36.
36) Aeberli I, Zimmermann MB, Molinari L, Lehmann R, l'Allemand D, Spinas GA, Berneis K. Fructose intake is a predictor of LDL particle size in overweight schoolchildren. Am J Clin Nutr 2007; 86:1174-8.
37) Krayenbuehl PA, Wiesli P, Schmid C, Lehmann R, Spinas GA, Berneis K. Insulin sensitivity in type 2 diabetes is closely associated with LDL particle size. Swiss Med Wkly 2008; 138: 275-80.
38) Gazi I, Tsimihodimos V, Filippatos T, Bairaktari E, Tselepis AD, Elisaf M. Concentration and relative distribution of low-density lipoprotein subfractions in patients with metabolic syndrome defined according to the National Cholesterol Education Program criteria. Metabolism 2006;55: 885-91.
39) Julius U, Dittrich M, Pietzsch J. Factors influencing the formation of small dense low-density lipoprotein particles in dependence on the presence of the metabolic syndrome and on the degree of glucose intolerance. Int J Clin Pract 2007;61:1798-804.
40) Gentile M, Panico S, Jossa F, Mattiello A, Ubaldi S, Marotta G, et al. Small dense LDL particles and metabolic syndrome in a sample of middle-aged women. Findings from Progetto Atena. Clin Chim Acta 2008; 388:179-83.
41) Rizzo M, Pernice V, Frasheri A, Di Lorenzo G, Rini GB, Spinas GA, et al. Small, dense low-density lipoproteins are predictors of cardio- and cerebro-vascular events in subjects with the metabolic syndrome. Clin Endocr 2009; 70:870-5.
42) Davidson MH, Toth PP. Comparative effects of lipid-lowering therapies. Prog Cardiovasc Dis 2004; 73-104.
43) Rizzo M, Berneis K. The clinical significance of the size of low-density-lipoproteins and the modulation of subclasses by fibrates. Curr Med Res Opin 2007; 23:1103-1111.
44) Rizzo M, Berneis K. The clinical relevance of low-density-lipoproteins size modulation by statins. Cardiovasc Drug Ther 2006; 20:205-217.
45) Rizzo M, Berneis K, Spinas GA, Rini GB, Kapur NK. Quantitative and qualitative effects of rosuvastatin on LDL-cholesterol: what is the clinical significance? Int J Clin Pract 2009; 63:478-85.
46) Rosenson RS, Otvos JD, Freedman DS. Relations of lipoprotein subclass levels and low-density lipoprotein size to progression of coronary artery disease in the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial. Am J Cardiol. 2002;90(2):89-94.
47) Miller BD, Alderman EL, Haskell WL, Fair JM, Krauss RM. Predominance of dense low-density lipoprotein particles predicts angiographic benefit of therapy in the Stanford Coronary Risk Intervention Project. Circulation 1996; 94:2146-2153
48) Zambon A, Hokanson JE, Brown BG, Brunzell JD. Evidence for a new pathophysiological mechanism for coronary artery disease regression: hepatic lipase-mediated changes in LDL density. Circulation 1999; 99:1959-64.
49) Marais AD. Therapeutic modulation of low-density lipoprotein size. Curr Opin Lipidol 2000; 11:597-602.
50) Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Circulation 1992; 85:37-45.
51) Tenkanen L, Manttari M, Manninen V. Some coronary risk factors related to the insulin resistance syndrome and the treatment with gemfibrozil. Experience from the Helsinki Heart Study. Circulation 1995; 92:1779-1785.
52) Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high density lipoprotein cholesterol: Veterans Affairs High-density Lipoprotein Cholesterol Intervention Trials Study Group. N Engl J Med 1999; 341:410-418.
53) Keech A, Simes RJ, Barter P et al.; FIELD study investigators. Effects of long-term

fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005; 366:1849-61
54) Wierzbicki AS. Fibrates after the FIELD study: Some answers, more questions. Diab Vasc Dis Res 2006;3:166-71.
55) Hiukka A, Leinonen E, Jauhiainen M, Sundvall J, Ehnholm C, Keech AC, Taskinen MR. Long-term effects of fenofibrate on VLDL and HDL subspecies in participants with type 2 diabetes mellitus. Diabetologia 2007; 50: 2067-75.
56) Genest J, Frolich J, Fodor G, McPherson R, the Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management of dyslipidemias and the prevention of cardiovascular disease: summary of the 2003 update. JAMC 2003;169:921- 4.
57) Barter PJ, Ballantyne CM, Carmena R, Castro Cabezas M, Chapman MJ, et al. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty person/ ten-country panel. J Intern Med 2006;259: 247-58.
58) Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, Witztum JL. Lipoprotein management in patients with cardio-metabolic risk: conference report from the American Diabetes Association and the American College of Cardiology Foundation. JACC 2008;51: 1512-245.
59) Contois JH, McConnell JP, Sethi AA, Csako G, Devaraj S, Hoefner DM, Warnick GR; AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. Apolipoprotein B and cardiovascular disease risk: position statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. Clin Chem 2009; 55:407-19.
60) Superko HR. Advanced lipoprotein testing and subfractionation are clinically useful. Circulation 2009; 119:2383-95.
61) Griffin BA, Caslake MJ, Yip B, Tait GW, Packard CJ, Shepherd J. Rapid isolation of low density lipoprotein (LDL) subfractions from plasma by density gradient ultracentrifugation. Atherosclerosis 1990; 83:59-67.

Lipids and Lipoproteins Division of AACC – In the Beginning…

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In the beginning there was darkness and from the darkness emerged a fatty substance that was unknown among men. Scientists studied the substance and found it present in the cells of animals and humans. An abnormal amount of this chemical in both humans and animals was associated with an increased risk of heart disease and sudden death. It was discovered that this fatty material was deposited in large quantities on the surface of the vessels. These vessels are called arteries and the surface is coated with endothelial cells where the build up of fatty substance is called plaque. Scientists worked feverishly (sweaty) and tirelessly (tread was running low) to identify this unknown substance. Soon mad scientists were successful at identifying this substance that was responsible for destroying lives at an early age and it was called cholesterol. Before long, a special group of individuals was united with the task to learn more about this substance and to distribute pertinent information to all its members. Thus, was born the Lipids and Lipoproteins Division of AACC and the *The Fats of Life*, a newsletter to keep the membership informed of news and events that were happening in the world of lipids.

Ok, so this might be a little stretch of the imagination to believe that the above has any shred of truth as to how and when the L&LD and *The Fats of Life* were brought into the world of AACC. Actually, an application was authored by several key individuals (the names my weak mind recalls as key contributors in this effort include GR Warnick, JD Artiss, Bennie Zak, HK Naito, DA Wiebe, and GR Cooper) and the application was submitted to AACC for consideration of a new AACC division on March 31, 1986. The Board of Directors of AACC accepted and approved the provisional status of L&LD at their December 1986 meeting. In 1989, the term "provisional" was removed and the L&LD was an official division of AACC. Twenty years – where has the time gone?

The early leadership of L&LD included G. Russell Warnick as Chairman, myself as Secretary, Joseph D. Artiss as Treasurer, and Herbert K. Naito as Member-at-Large. My memory remains cloudy as to exactly how these individuals were selected to these lofty positions, but I am almost certain that there was not an open election process involved. Arm-twisting, probably, but certainly my vote wasn't counted. As secretary, I also inherited the task to produce and edit our newsletter, *The Fats of Life*. The aforementioned management team remained intact for the three years that L&LD was designated as a provisional division of AACC. Elections were held during the fall of 1989 and we elected Chair-elect, Secretary and a Treasurer (not sure what happened to the Member-at-Large). Therefore, our leadership counsel was now composed of a Past-Chair (Russ), Chair (myself), Chair-elect (Gary Myers), Secretary (Judith McNamara), and Treasurer (Joseph Artiss). This is where my memory cells have failed me again because I'm not sure whether the Chair was truly elected or appointed and only our Chair-elect was selected by our membership. Another significant change in our leadership roles had taken place during the summer of 1988, Nader Riafi, a clinical chemist at Children's Hospital in Washington D.C., accepted the duties and responsibilities as Editor for *The Fats of Life* (I wonder if this could lead to bigger and better things to come?). These were the early days of L&LD and our Division was off to a fast start.

Timing of the formation of the L&LD coincided with a couple of major events that occurred around this same timeframe. First, the results of the NIH-funded Lipid Research Clinic's primary prevention trial were published in 1984. The LRC study clearly demonstrated that lowering plasma cholesterol in men reduced their risk for a cardiovascular event. Lowering total cholesterol by 1% reduced the individual's risk of CHD by 2%, an

outcome that supported the claims that cholesterol played a major role in the development of cardiovascular disease. Next, NIH established the National Cholesterol Education Program (NCEP). NCEP was given several goals and the three prominent ones were to: 1) establish an Adult Treatment Panel that developed uniform guidelines for physicians to use when treating patients with hypercholesterolemia, 2) increase the public's awareness about the health concerns related to hypercholesterolemia, and 3) improve the laboratory performance for measuring cholesterol. This last goal was one that L&LD and our members would have a significant impact and participation to ensure its success.

Many of our members played key leadership roles on committees, such as the NCEP Laboratory Standardization Panel, or as part of the Cholesterol Method Reference Laboratory Network (CMRLN) that provided the basis and foundation to improve the routine methods used to monitor patient's cholesterol status. Our L&LD had a major role in supporting forums at national AACC meetings where many of the issues related to cholesterol or lipid analyses were discussed openly to seek ways in which improvement could be achieved. In fact, the first issue, Volume I of *The Fats of Life*, published June 1987, promoted an L&LD conference to be held on Sunday afternoon at the national AACC meeting in San Francisco. The title of the conference was "Issues of Lipid Standardization and Reference Materials." The meeting was divided into two sessions; in the first session speakers were invited from NCEP (Herb Naito), CDC (Gary Myers), CAP (Al Hartmann), the National Reference System – Cholesterol (Ray Vanderlinde), and Russ Warnick to discuss the needs to improve cholesterol laboratory performance. During the second session, speakers representing industry, such as Nathan Gochman (Beckman Instruments), Wendell O'Neil (DuPont), Jack Levine (Technicon), Robert Bodden (American Dade) and Neil Greenberg (Eastman Kodak), discussed issues related to their own instruments. The conference was extremely well attended and through L&LD's efforts the conference brought together major players that were needed to put their resources together to improve our laboratories' ability to provide precise and accurate measurements of serum cholesterol. These manufacturer workshops became quite popular at AACC meetings and during the next few years our division was joined by NCCLS to co-sponsor the events. The first four workshops dealt with issues related directly to cholesterol analysis and ways in which our various laboratory methods could be improved. Manufacturers, government agencies (CDC, NIST, FDA), and clinical laboratory organizations (AACC, CAP, NCCLS) played important roles in these activities to overcome some of the issues related to cholesterol testing and cholesterol standardization. Our Division was instrumental in bringing together key individuals and groups with a common goal to overcome specific issues related to generating reliable cholesterol data for patients.

One yardstick to judge the success of an AACC division is the growth of the membership over the first few years when the division was given provisional status. Had the AACC members failed to sign up as members of the L&LD and shown little interest in what our Division had to offer, then it is unlikely that the Board of Directors would have granted permanent status for our Division. Our growth during these early years was as hoped and our Division grew from an initial membership of 207 in 1987 to 383 in 1988 and 458 by 1989. I suspect this helped influence the final decision to change our status as a provisional group. Today, our membership of the Lipoproteins and Vascular Diseases Division is close to 485 members, thus there are still quite a few individuals that find membership in our group to be worthwhile.

So where did we come up with the name for our newsletter? As secretary for our Division during those early years, I was assigned, or given the opportunity, to produce a newsletter for our members. Using a newly acquired Macintosh 512K computer and its graphics capability, a newsletter (Volume 1, number 1) was sent to all members during June 1987.

I used "*Fats of Life*" as the name for our newsletter. However, I would not be honest if I took sole

credit for this. Actually, I was taking a biochemistry class several years earlier at the University of Iowa where an instructor had used this phrase to introduce a chapter on lipids. I'm not sure why the phrase stuck with me so long, but it seemed to "fit like a glove." A copy of this first newsletter appears in this issue of the *FATS* and will, therefore, find a place in our archives for anyone wishing to see how far we have advanced. The initial newsletter doesn't come close the quality or professionalism that goes into generating our current product thanks to the contribution of the individuals that serve on the Editorial Board for the Newsletter.

Next question: who is responsible for the original logo for our Division? The answer to this question can be found be found in Volume 1, Number 2 edition of our newsletter, published in January 1988. Figure 1 shows our first logo, which was introduced in the second newsletter, and it was acknowledged that Donald Renaud from Ottawa, Ontario designed it.

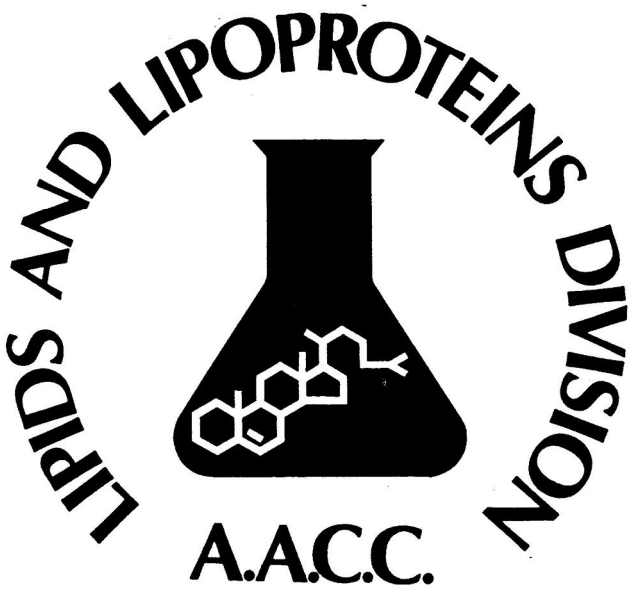

Figure 1. First L&LD logo, which was introduced in the second *Fats of Life* newsletter.

This logo was prominently displayed on the majority of our newsletters and was also placed on awards that our Division bestowed on deserving members. Figure 2 is a proposed logo that ranked second, but was never used. A few of the other logos that have been used by our Division are also shown below (Figures 3 and 4).

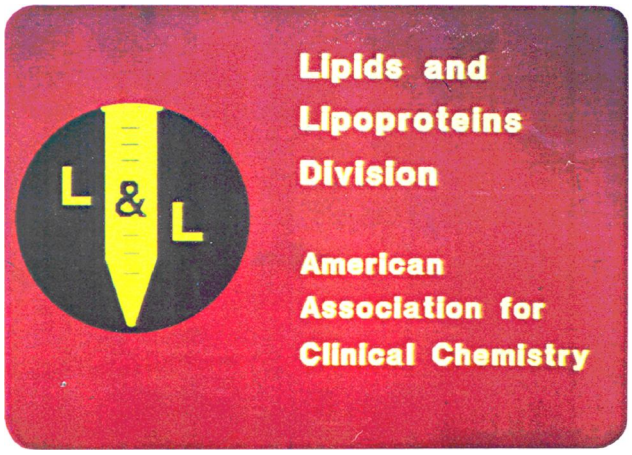

Figure 2. A runner up for the first logo of our Division (unknown submission).

Figure 3. Logo associated with our Newsletter during the late 1990s early 2000s, and still used today in the footer.

Clearly our Lipoproteins and Vascular Diseases Division has and continues to be active in the areas of lipids and lipoproteins plus numerous other AACC activities. I can look back on my own career and appreciate how valuable and enriching my membership in our Division has been for my

Figure 4. Current logo of the Lipoproteins and Vascular Diseases Division.

professional advancement. I have developed special friendships and participated in unique opportunities over the last several years and many are directly related to my involvement in our organization. I encourage all our members, young and old to get involved and active in our Division – the benefits and rewards will be amazing.

Faith Clendenen, LVDD Secretary

Executive Meeting Teleconference
Wednesday, April 8, 2009

Attendees: Gyorgy Csako (Chair), John Contois (Editor, Fats of Life), Faith Clendenen (Secretary), Dan Hoefner (Information Officer), Amar Sethi, Joe McConnell (Past Chair), Russell Warnick (Editor, Fats of Life), Rose Romeo (Treasurer)

Agenda:

1. Approval of minutes from November 25, 2008 (Teleconference). **Approved as submitted.**

2. The Fats of Life

- Spring Issue by April 15th, Guest Editorial by Don Wiebe to be moved to Summer (see below). Minutes from the Executive Board Meeting must be included as required by the By-Laws. **Faith to get minutes to John Contois before April 15th.** Three other articles scheduled but not yet submitted.
- Summer issue dedicated to our 20th anniversary. Trying to get a history of the division from Don Wiebe. Articles will be submitted that reflect the history and contributions of the Division, including something from Gerald Cooper. Get a list of founders of the division and include that in the FOL and invite them to the Monday Night meeting. Include pictures of early meetings if there are any available.

3. Annual Division Feedback for LVDD from Steve Kazmierczak, PhD, DMG Chair. Very encouraging information. The accompanying report provides a summary of our division's strengths from the DMG perspective and outlines areas of opportunity for 2009. We are asked to consider the "challenges and opportunities" section of the attached report as you make plans for next year.

4. Annual Meeting

Contributions for the Monday Night Meeting. Ortho to give $10000 contribution for the Monday Meeting. Helena Labs has already donated $1000 to the division; check should be at National. They have requested that CE's be available for this meeting; **(Faith and Penny working on this.)** Dinner fee is $50 but cost is $100/head. It is being limited to members only. In view of the generous donations from Ortho and Helena, the meeting size could be expanded. **Comment (from Penny Jones):** Our online registration system cannot identify membership at the division level. That means we will not be able to allow online registration for the Monday dinner and Lipoproteins forum. Registration for these events will have to be by paper. Also, to prevent confusion (since non division members have been allowed to participate in the past), our Customer Service Manager recommends **not** putting this on the Annual Meeting registration order form. That means promoting it separately to division members only." How this would be handled was not discussed during the teleconference.

Meeting rooms, already arranged, are listed here:

Sunday Board and Business Meeting: Sunday, July 19, 8:00am—11:00am, Hyatt Regency Chicago Hotel (Columbian Room)

Monday Dinner Meeting: Current Topics in Cardiovascular Disease, Monday, July 20, 5:30pm—9:30pm, Hyatt Regency Chicago Hotel (Columbus Hall A, B, C, D)

Tuesday Night Dinner: INTERNATIONAL LIPOPROTEIN STANDARDIZATION FORUM, Tuesday, July 21, 6:00pm—9:30pm, Hyatt Regency Chicago Hotel (Columbus Hall K, L)

5. Annual Business Meeting as required by By-Laws: Sunday morning meeting or Monday night meeting? Room size limited for Sunday morning, but Monday night too busy. The consensus is to **use Sunday morning meeting as the annual business meeting**, increase room size and food obtained. **Unanimously approved.**

6. Awards:

- 2009 Zak Award (Contributions to Science): Joe McConnell
- Cooper (Contributions to Technology) Award is due in 2010
- 2009 Pacific Biometric Research Foundation Award: Dr. Chong Yuan (California)
- Award for FOL Best Article in 2008: To be decided by Nomination Committee based on 5 candidate articles selected by editors. **Need this by May 1st.**
- Our travel award for young foreign clinical chemists has been discontinued due to budget constraints.
- LVDD poster awards. Need to arrange to do the poster awards. Amar Sethi has volunteered to help with the poster award. We will make the decision based on the abstracts and have the awards (ribbons) on the posters and checks in advance, if possible. **Rose will follow up on ribbons and timing of checks. Faith to send awardee info to Rose, received from Gyorgy.**

7. Accent Credit for Annual Meeting: Faith and Penny to get in place.

8. Elections in 2009:
This year Nominating Committee members are up for election. Need names for nominating committee, and Treasurer and Secretary are technically both in their second year, although they are not currently elected in alternate years. **Gyorgy will send email of rules regarding alternating years of Treasurer and Secretary.** Secretary (Faith) has offered to extend an additional year, and ask for one of the Nominating Committee to extend a year also. **Unanimously approved.** Urgently needed nominations for Treasurer and Nominating Committee member. By-laws require two names for each position.

10. **.Next Teleconference:** Need additional Teleconference in mid-May. Open items to be discussed: 1) shared meeting with a local section, possibly in the fall, 2) discuss changes to By-Laws, 3) Names for nominations, and 4) 20th Anniversary issues. Please review the By-Laws (attached) before the next meeting.

LIPOPROTEINS and VASCULAR DISEASES DIVISION BY-LAWS

The name of this organization will be the Lipoproteins and Vascular Diseases Division (referred to below as DIVISION) of the American Association for Clinical Chemistry (referred to below as AACC).

The purpose of the DIVISION will be the provision of a focus for interaction among AACC Members with interests in lipids, lipoproteins and vascular diseases and a forum for communication among laboratorians, clinicians, other scientists and representatives of industry; promotion of activities which lead to improvements in the general level of knowledge in measurement technology, in standardization of methods, and in interpretation/usefulness of lipid/lipoprotein results; and enhancement of the professional image and status of the AACC.

A. The DIVISION will support and facilitate programs which will help to achieve the stated purposes.

B. The DIVISION will review/evaluate existing and new lipid/lipoprotein methodologies/technologies and provide information to the membership.

C. The DIVISION will submit suggestions for educational sessions to the Organizing Committee of each Annual Meeting of the AACC.

D. The DIVISION will cooperate with local sections, other divisions, and other professional groups to co-sponsor meetings and to work jointly for the advancement of science, medicine, and technology.

E. The DIVISION will assist or coordinate assignments for speakers and disseminate educational materials dealing with various aspects of the lipid and lipoprotein field to groups wishing these services.

F. The DIVISION will publish a newsletter providing information about DIVISION meetings, significant events, and selected topics of current interest. This newsletter will be provided to all DIVISION Members.

G. The DIVISION will hold a business meeting at the Annual AACC Meeting each year, with opportunity for discussion and review of activities.

Anyone who is a current Member of the AACC as defined by the Association Bylaws, Article I, may become a DIVISION Member by contacting the DIVISION or the AACC National Office and by paying the DIVISION dues.

A. The officers of the DIVISION will be Members in good standing of the AACC and the DIVISION. Only officers and their delegates may represent the DIVISION in official capacities.

B. The officers of the DIVISION will be a Chair, who will serve two (2) years; a Chair-Elect, who will serve two (2) years and be designated as Chair for the following two (2) years; a Secretary, a Treasurer and an Information Officer, each of whom will serve for two (2) years. The Chair-Elect will be elected every other year and the Secretary and Treasurer will be elected in alternate years and will not serve for more than two (2) consecutive terms, or four (4) consecutive years. The Information Officer will be appointed by the Chair. The Chair will not be eligible for re-election to the office of Chair-Elect until one year has lapsed since his/her last term of office. The powers and duties of the officers will be those usually vested in their respective positions or specified by the Bylaws.

C. The duties of the various officers will be as follows:

1. Chair

a. Function as the executive officer for the DIVISION.
b. Organize and preside at all official meetings of the DIVISION.
c. Coordinate Committee and general DIVISION activities.
d. Appoint Committee chairs subject to the approval of the Executive Committee.
e. Coordinate preparation of the annual report and the annual budget.
f. Serve as an ex-officio member of each Committee.
g Serve as Chair of the Nominating Committee.

2. Chair-Elect

a. Preside at meetings in the absence of the Chair.
b. Act for the Chair in case of his/her absence or disability.
c. Serve as Chair of the Program Committee.
d. Direct long-range planning activities of the DIVISION.

3. Secretary

a. Keep minutes of all meetings of the DIVISION at which business is conducted, and submit them to the Chair for approval.
b. Maintain the minutes of all meetings as a record and transmit them to the succeeding Secretary.
c. Submit approved minutes to the Newsletter Editor for publication in the newsletter.
d. Carry out correspondence of the DIVISION as delegated by the Chair.
e. Distribute notices of meetings, ballots, and election results to the membership and receive completed election ballots.
f. Assist the Chair with the preparation of the annual report.

4. Treasurer

a. Receive and distribute funds authorized in the DIVISION budget.
b. Maintain accurate and current records of all credits, debits, and balances and transmit them to the succeeding Treasurer.
c. Present a financial report of receipts, disbursements, and current balances at official meetings.
d. Assist the Chair with the preparation of the annual budget and report.

5. Information Officer

a. Serve as DIVISION Web Master.
b. Collaborate with Newsletter Editor on projects as needed.
c. In conjunction with the AACC, keep consumer web page current.

ARTICLE VI. Committees

Standing Committees will include the Executive Committee, the Program Committee, the Nominating Committee, and the Membership Committee.

A. Executive Committee

1. Will consist of the DIVISION Chair, Chair-Elect, Secretary, Treasurer, and Information Officer.
2. Will have authority to act on all matters concerning the DIVISION.
3. Will meet at least once a year.
4. Will consist of a quorum, necessary to conduct DIVISION business, of at least three (3) of the five (5) members.
5. May invite the Newsletter Editor and the Chairs of ad hoc committees to participate as non-voting representatives.

B. Program Committee

1. Will consist of a Chair, who will be the current Chair-Elect of the DIVISION, and members to be appointed annually as deemed necessary by the Committee Chair.
2. Will plan, schedule, and coordinate workshops, seminars and other educational activities of the DIVISION.
3. Will provide a summary of activities to the DIVISION Chair for inclusion in the annual report.

C. Nominating Committee

1. Will consist of a Chair, who will be the Chair of the DIVISION, and two elected Members. The elected Members will serve for two (2) years; one Member will be elected each year from a list of two (2) candidates submitted by the Nominating Committee as described in Section C, 3 below. Members of the Nominating Committee may not succeed themselves and are ineligible to be nominated as an officer, for a period of one (l) year following the end of their term on the Committee.
2. Will prepare a slate of candidates for the elected offices as described in ARTICLE V. Candidates will have given prior consent to serve, if elected.
3. Will report the slate of nominees to the DIVISION Secretary by March 15th of each year.
4. Initial Nominating Committee will be selected by the Executive Committee of the Provisional Division.

D. Membership Committee

1. Will consist of a Chair, who will be appointed by the DIVISION Chair with the approval of the Executive Committee, and members to be appointed annually as deemed necessary by the Committee Chair.
2. Will maintain an accurate list of names and addresses of all members.
3. Will devise and implement strategies to recruit new members and retain current members.
4. Will provide a summary of activities to the DIVISION Chair for inclusion in the annual report

E. Finance Committee

1. Will consist of a Chair, who will be appointed by the DIVISION Chair with the approval of the Executive Committee, the DIVISION Treasurer, and members to be appointed annually as deemed necessary by the Committee Chair.
2. Will solicit funds to support DIVISION activities and will recognize donors.

F. Other Committees

Other ad hoc committees will be convened as deemed necessary. The Chair of each committee will be appointed by the DIVISION Chair with approval from the Executive Committee.

ARTICLE VII. Terms of Office, Elections, and Vacancies

A. Terms of Office

Terms of office will begin on January 1 and end on December 31 of each year.

B. Elections

1. Elections will be by mail or electronic ballot, conducted so as to maintain secrecy.
2. The Chair of the Nominating Committee will notify the Secretary of the slate of candidates by March 15th of each year. The nominees will be those members selected by the Nominating Committee and who have agreed to serve prior to having their names placed on the ballot.
3. The candidates will provide biographical sketches for the ballots to the Secretary by April 1.
4. The Secretary will distribute by May 1 a ballot, consisting of a slate prepared by the Nominating Committee, to each member of the DIVISION. This ballot will show the positions to be filled, the nominees for each office, and a provision for write-in votes.
5. The deadline for receipt of valid ballots will be June 1. Completed ballots will be received by the DIVISION Secretary and opened and tallied by two non-candidates appointed by the Secretary.
6. Nominees receiving a plurality of votes will be elected. In the event of a tie vote, the election will be decided by secret ballot of the Executive Committee.
7. The Secretary, by June 15, will then report the results to the DIVISION Chair, who will notify the nominees.
8. The Secretary will notify the Executive Committee, the membership, and the National Office.
9. In the event that an officer is not elected by January 1, the preceding officer will continue to serve until relieved by the duly elected succeeding officer.

C. Vacancies

1. Resignation of officers, except the Chair, will be submitted in writing to the Chair. The resignation of the Chair will be submitted in writing to the Executive Committee.

2. In the event of a vacancy in the office of Chair, the Chair-Elect will succeed the Chair for the remainder of the unexpired term and for the following fiscal year. In the event of a vacancy in the office of Secretary or Treasurer, or among the elected Members of the Nominating Committee, the incumbent Executive Committee will appoint a qualified Member to discharge the duties of that office until January 1st following the next regularly scheduled election to fill that vacancy. In the event of a vacancy in the office of Chair-Elect, the Nominating Committee will transmit within thirty (30) days of the vacancy to the Secretary, a list of nominees for election. This election process will be completed as quickly as practical, as described in ARTICLE VII, Section B. The Chair will fulfill the Chair-Elect's responsibilities in the interim.
3. An officer may be impeached following, first, a majority vote by the Executive Committee, and second, a mail-ballot vote by the Membership. A two-thirds majority of the votes cast is required to effect the removal from office of one of the elected officers.

ARTICLE VIII Finances

A. The fiscal year of the DIVISION will coincide with that of the AACC, beginning on January 1, and ending on December 31.

B. DIVISION dues, established by the Executive Committee, will be collected by the National Office with regular AACC membership dues.

C. The DIVISION will follow the rules established by the AACC Finance Committee for expenses (living and travel), honoraria (amount and eligibility), and registration fees.

D. The Chair and Treasurer of the DIVISION will prepare an annual report as requested by the National Organization to be submitted to the AACC Liaison and Board of Directors through appropriate channels. The report will include the status of the DIVISION, activities and accomplishments, financial notation of sources of revenue and purposes for which they were used and the organizations to be solicited in the coming year.

E. In the event that the DIVISION is dissolved, all funds remaining after the payment of debts will be transferred to the AACC. In no event will any funds of the DIVISION inure to the benefit of any DIVISION Member either during the life of the DIVISION or after its dissolution.

ARTICLE IX. Adoption and Amendment to the Bylaws

A. Amendments of these Bylaws may be proposed by a majority vote of the Executive Committee, by a petition signed by at least 10% of the Members in good standing, or by a duly passed motion at any official business meeting. Proposals for adoption or amendments of the Bylaws will be distributed to each Member in good standing by the Secretary within 45 days of receipt.

B. Adoption and amendments of the Bylaws will require an affirmative vote by two-thirds of the votes received. If the proposal does not receive the required number of votes within 30 days after the proposal is distributed, then such proposal will lapse.

C. These Bylaws will become effective at the time of their adoption.

Gyorgy Csako, MD

Title: Low-density lipoprotein cholesterol concentrations and death due to intraparenchymal hemorrhage: the Ibaraki Prefectural Health Study.
Authors: Noda H, Iso H, Irie F, Sairenchi T, Ohtaka E, Doi M, Izumi Y, Ohta H.
Journal: Circulation. 2009 Apr 28;119(16):2136-45. Epub 2009 Apr 13.
Comment: Since most of our effort involves lipid lowering, it is interesting to note that low lipid levels may not always be advantageous. A possible association between low total cholesterol levels and increased risk of intraparenchymal hemorrhage (hemorrhagic stroke), which has a low survival rate and a high risk of disability, was reported first 3 decades ago. Since then, several, but not all, studies confirmed such an association. Hemorrhagic stroke has unique pathological and epidemiological characteristics that distinguish it from coronary heart disease (CHD). It is caused primarily by hypertension and, as observed earlier, possibly by low concentrations of low-density lipoprotein-cholesterol (LDL-C). This large Japanese population-based study cohort study further examined the association between low levels of LDL-C and risk of intraparenchymal hemorrhage. A total of 30,802 men and 60,417 women, 40 to 79 years of age with no history of stroke or coronary heart disease, completed a baseline risk factor survey in 1993 under the auspices of the Ibaraki Prefectural Health Study. Systematic mortality surveillance was performed through 2003, and 264 intraparenchymal hemorrhage deaths were identified. LDL-C levels were calculated with the Friedewald formula. Persons with LDL-C >140 mg/dL had half the sex- and age-adjusted risk of death due to intraparenchymal hemorrhage of those with LDL-C <80 mg/dL. After adjustment for cardiovascular risk factors, the multivariable hazard ratio compared with persons with LDL-C <80 mg/dL was 0.65 (95% CI 0.44-0.96) for those with LDL-C 80 to 99 mg/dL, 0.48 (0.32-0.71) for 100 to 119 mg/dL, 0.50 (0.33-0.75) for 120 to 139 mg/dL, and 0.45 (0.30-0.69) for >140 mg/dL. These inverse associations were not altered substantially after the exclusion of persons with hypertriglyceridemia, after analysis with a Cox proportional hazard model with time-dependent covariates, or in sensitivity analysis for the potential effect of competing risks. There was a U-shaped relationship between LDL-C and combined death due to intraparenchymal hemorrhage and CAD, with a nadir at LDL-C levels of 120-139 mg/dL (3.10-3.61 mmol/L) because these 2 outcomes have an opposite direction in the association with LDL-C. The authors concluded that low LDL-C levels indeed are associated with elevated risk of death due to intraparenchymal hemorrhage and suggested that this relationship likely is causal. An accompanying editorial (see below) further analyzed the results of this study and its relevance to cholesterol (LDL-C)-lowering therapy.

Title: The complex relationship between cholesterol and brain hemorrhage. (Editorial on the article by Noda *et al.* Circulation. 2009 Apr 28; 119(16):2136-45)
Author: Goldstein LB.
Journal: Circulation. 2009 Apr 28;119(16):2131-3.
Comment: Commenting on the findings of Noda *et al.*, Dr. Goldstein pointed out that the relationship between lipid levels and stroke is complex: although low, usual total cholesterol and LDL-C levels in persons free of cardiovascular disease or stroke appear to be associated with a higher risk of brain hemorrhage, this does not mean that treating patients with vascular disease with lipid-lowering medications increases risk. Even achieving very low levels of LDL-C (i.e., <40 mg/dL or <64 mg/dL) with statins in patients with coronary heart disease was not associated with an increased risk of brain hemorrhage. On the other hand, the situation is somewhat more complicated in patients with a prior history of stroke in whom the overall treatment-related benefit in reducing the risk of the primary end-point (fatal or non-fatal stroke) was partially attenuated by a treatment-related increase in brain hemorrhage. Thus, the relationship between statin therapy and the risk of brain hemorrhage may be different in patients with a history of cerebrovascular disease (who overall still benefit from statin treatment) compared with those without such a history. While the epidemio-

logical data based on usual total cholesterol and LDL-C levels suggest an association between low levels and increased risk of brain hemorrhage, there is no evidence of a relationship between cholesterol levels and bleeding risk in patients with coronary heart disease whose lipid levels have been lowered medically. Dr. Goldstein also emphasized that establishing causality based on statistical associations from observational studies is always hazardous. In fact, the lack of a relationship between low, usual total cholesterol and LDL-C and higher risk of brain hemorrhage in persons whose total cholesterol and LDL-C have been lowered therapeutically argues against causality.

Title: Modification of the association between alcohol drinking and non-HDL cholesterol by gender.
Authors: Wakabayashi I, Groschner K.
Journal: Clin Chim Acta. 2009 Jun 27;404(2):154-9. Epub 2009 Mar 29.
Comment: A possible role of alcohol consumption for reducing cardiovascular risk has been long debated. The authors of this article studied the relationship between habitual alcohol drinking and serum non-HDL cholesterol (non-HDL-C, a strong predictor of cardiovascular diseases) in a Japanese population. Healthy male subjects (n = 27,005) and female subjects (n = 16,805) were divided into 5 groups by average daily ethanol intake. Serum non-HDL-C level and prevalence of serum high non-HDL-C ($\geq$170 mg/dL) were compared among the groups. It was found that non-HDL-C level and prevalence of high non-HDL-C become lower as alcohol intake increases. The threshold alcohol intake in the drinker groups showing significantly lower non-HDL-C level and significantly lower prevalence of high non-HDL cholesterol, compared with those in non-drinkers, was lower in women (<10 g/d) than in men ($\geq$10 and <20 g/d). Odds ratios of each drinker group vs. the non-drinker group for high non-HDL-C became lower as alcohol intake increased. The odds ratio of each drinker group vs. the non-drinker group for high non-HDL-C tended to be lower in women than in men. Thus, even light drinking is sufficient to significantly lower serum non-HDL-C and that this effect of alcohol drinking on non-HDL-C is more pronounced in women than in men.

Title: The association of 83 plasma proteins with CHD mortality, BMI, HDL- and total-cholesterol in men: applying multivariate statistics to identify proteins with prognostic value and biological relevance.
Authors: Heidema AG, Thissen U, Boer JM, Bouwman FG, Feskens EJ, Mariman EC.
Journal: J Proteome Res. 2009 Jun 5;8(6):2640-2649. Epub 2009 Apr 7.
Comment: Recent technical advances in proteomics such as multiple assays provide the opportunity to simultaneously measure the concentrations of a large number of proteins in plasma. This enables researchers to study the relationships of groups of proteins with the outcome of interest. In this study, the authors applied the multivariate statistical tool Partial Least Squares (PLS) to analyze the relative importance of 83 plasma proteins in relation to coronary heart disease (CHD) mortality and the intermediate endpoints body mass index, HDL-cholesterol and total cholesterol. PLS takes the information of all proteins into account with respect to a certain end-point and is able to handle not only large numbers of variables in moderate to small sample sizes, but also the presence of multicolinearity among the proteins. From a Dutch monitoring project for cardiovascular disease risk factors men who died of CHD between initial participation (1987-1991) and end of follow up (January 1, 2000) (N=44) and matched controls (N=44) were selected. Baseline plasma concentrations of proteins were measured by a multiplex immunoassay. Applying PLS, the authors identified 15 proteins with prognostic value for CHD mortality and sets of proteins associated with the intermediate endpoints. Subsequently, sets of proteins and intermediate endpoints were analyzed together by another statistical tool (Principal Components Analysis or PCA). PCA constructs factors that maximally explain the variance in the data, without relating the factors to another outcome variable (or a set of outcome variables). PCA analysis indicated that proteins involved in inflammation explained most of the variance, followed by proteins involved in

metabolism and proteins associated with total cholesterol. This study is one of the first in which the association of a large number of plasma proteins with CHD mortality and intermediate endpoints is investigated by applying multivariate statistics, providing insight in the relationships among proteins, intermediate endpoints and CHD mortality, and a set of proteins with prognostic value.

Title: The HDL proteome: a marker--and perhaps mediator--of coronary artery disease.
Author: Heinecke JW.
Journal: J Lipid Res. 2009 Apr;50 Suppl:S167-71. Epub 2008 Dec 5.
Comment: One important cardioprotective function of HDL is to remove cholesterol from lipid-laden macrophages in the artery wall. HDL also exerts anti-inflammatory effects that might inhibit atherogenesis. However, HDL has been proposed to be dysfunctional in humans with established coronary artery disease (CAD), though the underlying mechanisms are unclear. Therefore, the author used mass spectrometry to investigate the roles of HDL proteins in inflammation and cardiovascular disease. Shotgun proteomic analysis identified multiple complement regulatory proteins, protease inhibitors, and acute-phase response proteins in HDL, strongly implicating the lipoprotein in inflammation and the innate immune system. Moreover, mass spectrometry and biochemical analyses demonstrated that HDL3 from subjects with clinically significant CAD was selectively enriched in apolipoprotein E, suggesting that it carries a distinctive protein cargo in humans with atherosclerosis. HDL from CAD subjects also contained markedly elevated levels of chlorotyrosine and nitrotyrosine, two characteristic products of myeloperoxidase, indicating that oxidative damage might generate dysfunctional HDL. Aggressive lipid therapy with a statin and niacin remodeled the HDL proteome to resemble that of apparently healthy subjects. Collectively, these observations indicate that quantifying the HDL proteome by mass spectrometry should help identify novel anti-inflammatory and cardioprotective actions of HDL and provide insights into lipid therapy.

Title: A "new" thematic series: mass spectrometry-based proteomics of lipid biology.
Author: Heinecke JW.
Journal: J Lipid Res. 2009 May;50(5):777-80. Epub 2009 Mar 2.
Comment: This editorial inaugurates JLR's "new" thematic series that highlights the applications of mass spectrometry to the study of proteins important in lipid metabolism and biology. Proteomics, a global approach to understanding protein expression, regulation, and function, transcends analysis of individual proteins. The author first briefly reviews mass spectrometry, a major tool of proteomic research, then the 5 topics of the "new" thematic series: proteomic analysis of lipid-protein complexes (see below in May issue), eicosanoid class of molecules (see below in June issue), emerging field of lipoprotein proteomics, the role of lipid rafts, and proteomics of lipid droplets.

Title: Thematic review series: Proteomics. Proteomic analysis of lipid-protein complexes.
Author: Vaisar T.
Journal: J Lipid Res. 2009 May;50(5):781-6. Epub 2009 Feb 19.
Comment: This is the first article in the JLR's "new" thematic review series. There is intense interest in comprehensive proteomic approaches for analyzing integral membrane proteins and lipoproteins. Lipid-associated proteins present a unique set of challenges to proteomic analysis. Key features of any MS analysis center on enriching biological material for proteins of interest, efficiently digesting them, extracting the resulting peptides, and using fractionation methods to comprehensively sample proteins or peptides by MS/MS. Integral membrane proteins have been extensively investigated by a number of well-validated protocols. In contrast, analysis of lipoprotein particles has received limited attention, and optimal approaches for comprehensive proteomic analysis are still being developed. Although the lessons learned while analyzing integral membrane proteins will undoubtedly benefit proteomic investigations of lipoproteins, unique features, especially the dominance of a few proteins in each particle type, will require innovative methods for detecting

low-abundance proteins in these protein-lipid complexes.

Title: Thematic review series: Proteomics. An integrated omics analysis of eicosanoid biology.
Authors: Buczynski MW, Dumlao DS, Dennis EA.
Journal: J Lipid Res. 2009 Jun;50(6):1015-38. Epub 2009 Feb 24.
Comment: This is the second article in the JLR's "new" thematic review series. Eicosanoids are signaling molecules made by oxygenation of twenty-carbon essential fatty acids (EFAs). They derive from either omega-3 (ω-3) or omega-6 (ω-6) EFAs. The ω-6 eicosanoids are generally pro-inflammatory; ω-3s are much less so. There are four families of eicosanoids—prostaglandins, prostacyclins, thromboxanes and leukotrienes. For each, there are two or three separate series, derived either from an ω-3 or ω-6 EFA. These series' different activities largely explain the health effects of ω-3 and ω-6 fats. Eicosanoids have been implicated in a vast number of devastating inflammatory conditions, including arthritis, atherosclerosis, pain, and cancer. Currently, over a hundred different eicosanoids have been identified, with many having potent bioactive signaling capacity. These lipid metabolites are synthesized *de novo* by at least 50 unique enzymes, many of which have been cloned and characterized. Due to the extensive characterization of eicosanoid biosynthetic pathways, this field provides a unique framework for integrating genomics, proteomics, and metabolomics toward the investigation of disease pathology. To facilitate a concerted systems biology approach, this review outlines the proteins implicated in eicosanoid biosynthesis and signaling in human, mouse, and rat. Applications of the extensive genomic and lipidomic research to date illustrate the questions in eicosanoid signaling that could be uniquely addressed by a thorough analysis of the entire eicosanoid proteome.