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Devastating Metabolic Consequences of a Life of Plenty: Focus on the Dyslipidemia of Overnutrition

Abstract

Although undernutrition and starvation continue to affect a substantial portion of the world's population, billions of people in both developed and developing countries are affected by the opposite problem: consumption of calories that exceed their daily energy expenditure, a condition of overnutrition. The body's response to a positive net energy balance is to store energy, predominantly as triglyceride molecules, in the subcutaneous and visceral fat compartments that expand and ultimately manifest in obesity. The body's fat depot, however, does not have an infinite capacity to store and expand, and at set points, which differ from individual to individual and are also influenced by ethnicity, energy substrates 'spill over', resulting in 'ectopic' fat storage in tissues and organs that are not typically major fat storage depots in lean individuals. A complex web of nutrient overload, chronic inflammation, hormonal action, mitochondrial dysfunction and insulin resistance, to mention some of the factors involved, results in devastating metabolic abnormalities that have far reaching implications for health and disease, leading ultimately to some of the most common chronic diseases of our time; i.e., diabetes mellitus, cancer, chronic liver disease and atherosclerosis. Given the complexity and wide-ranging manifestations of overnutrition (also referred to here as insulin resistant states), we will highlight a specific aspect of the condition, that of dyslipidemia. This review will draw mainly on knowledge acquired from whole body, integrative physiology research in animals and humans affected by overnutrition, and will demonstrate how these types of studies can shed light on our understanding of the pathophysiology of the typical dyslipidemia of obesity, insulin resistance and type 2 diabetes.

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Introduction – *in vivo* integrative physiology research; strengths and weaknesses.

The complexity of biological systems such as the human body can be overwhelming for the scientist intent on deciphering the functioning of such a system. Where do we even begin in trying to figure it all out? The reductive scientific method, in which molecules, cells and organs are isolated and studied *in vitro* or *ex vivo*, has yielded a treasure trove of information about the functioning of the human body, in health and disease. The molecular biology revolution has greatly accelerated the pace of that discovery. A major limitation, however, of these *in vitro* model systems, is the loss of the complex interactions between molecules, cells and organs, which cannot be completely replicated outside of the living organism. The complexity of the cross-talk and communication between various parts of the body, and the loss of that cross talk in *ex vivo* experimental model systems, may have a profound impact on the experimental results, not infrequently resulting in completely different or even opposite experimental findings, depending on the experimental conditions.

In vivo studies in animals and humans overcome some of these difficulties but have their own set of well appreciated limitations. Species other than the human are frequently utilized for biological experiments in order to enhance our understanding of the function of the human body in health and disease, for obvious practical reasons. There are major interspecies differences that may seriously limit the applicability of findings from animal models to the human. This is particularly true in studies of lipoprotein metabolism, in which key enzymes or lipid transfer factors that play a fundamental role in lipoprotein metabolism may be expressed at very different levels or may be completely absent in certain species but not in others. Studies in humans can only go so far in examining mechanisms of disease, since human studies are frequently limited by the inability to obtain internal organ tissue samples, to manipulate genes and to utilize small molecule activators and inhibitors or biologics to examine gain or loss of function, not to mention the inability to isolate and study mechanisms at the cell and molecular level. Despite the obvious limitations of *in vivo* integrative physiological studies, we will provide a few examples of how these types of studies can yield interesting results that enlighten us about the functioning of the human body. This brief review will focus on work from the author's lab and is not intended to be a comprehensive review of the many studies conducted by numerous outstanding research groups over the past few decades.

Why does overnutrition result in hypertriglyceridemia?

For a metabolite such as triglyceride (TG) that is constantly being produced and cleared from the body, steady state is maintained when production matches clearance. The concentration of the metabolite in a body compartment such as the circulation (referred to as the pool size) is determined by the balance between production and clearance. Elevation of triglycerides, or more specifically the triglyceride-rich lipoprotein particles (TRL), in the circulation results from one of two biological processes, an increase in production that exceeds its rate of removal or a reduction in its removal the magnitude of which exceeds its rate of production, or a combination of these two mechanisms. A variety of tracer techniques are available for evaluating TRL-TG and TRL-apoB-100 (a measure of VLDL particle production since there is one apoB-100 per VLDL particle) kinetics *in vivo*. Most contemporary methods make use of stable isotope-labeled tracers to measure the rate of incorporation and/or loss of the tracer into TG or apoB in TRL, often in combination with compartmental modeling analysis [1]. Application of this methodology to animal models or humans who have insulin resistance, obesity, metabolic syndrome or type 2 diabetes have demonstrated a consistent increase in secretion of TG or hepatically-derived VLDL-apoB-100 (the major TG-carrying particle in fasted, normolipidemic humans), with a less consistent reduction in clearance of these particles, the latter becoming a more prominent feature of poorly controlled type 2 diabetes [2]. We and others have demonstrated the important role played by free fatty acids (FFA) [3;4] and monosaccharides [5] in driving the production of hepatic and intestinal TRL production and the modifying role of hormones such as insulin [3;6;7], glucagon [8] and of gut peptides GLP-1 [9] and GLP-2 (manuscript in preparation) on this process (reviewed in [10-15]). These *in vivo* studies in the intact organism control for and take into account the compensatory factors that come into play in the body. *In vitro* and animal studies have, in most cases, been supported by our findings in humans [16-26], with the human studies providing clinical relevance to the animal work and the animal studies providing additional insights regarding the molecular regulation of TRL production in these states of overnutrition.

Approximately 10 years ago, utilizing the fructose-fed Syrian Golden hamster as a model of insulin resistance-induced hypertriglyceridemia, in collaboration with Dr. Khosrow Adeli (Department of Laboratory Medicine and Pathobiology, University of Toronto), we observed an increase in intestinally-derived chylomicron-apoB-48 TRL secretion that accompanies the well-appreciated overproduction of hepatic apoB-100-containing VLDL [27]. This increase in chylomicron production occurred even in fasted animals and reflected overproduc-

tion of lipid-poor apoB-48-containing particles by the intestine. This finding was later validated in humans, with insulin resistant humans shown to have an elevation of intestinal lipoprotein production [28]. Over the past decade we have devoted considerable attention to defining the regulatory mechanisms of chylomicron overproduction in insulin resistant states, with Dr. Adeli's laboratory taking predominantly a cell and molecular biological approach and my laboratory studying this phenomenon initially *in vivo* in the Syrian Golden hamster and more recently in humans. There are many similarities in nutrient and hormonal regulation of intestinal and hepatic lipoprotein production. We have recently reviewed these findings [12-15] and therefore will not expand upon them at length in this brief overview.

Does the intestine contribute in a quantitatively meaningful way to the dyslipidemia and atherogenicity of insulin resistant states?

It is important to appreciate that in fasted humans TRL apoB-48, a marker of intestinally derived chylomicron particles, is approximately one hundredth that of TRL apoB-100, a marker of hepatically-derived VLDL particles, and this proportion of particle numbers does not change dramatically in the postprandial state [29]. The triglyceride-carrying capacity of VLDL and chylomicrons differs markedly, however, with chylomicrons having the capacity to expand markedly in size in the postprandial state and transport far greater numbers of triglyceride (and cholesteryl ester) molecules per particle than VLDL, but the atherogenicity of the particles is felt to be related primarily to particle numbers, size and composition, all of which affect their capacity to cross the endothelial surface of arteries. The apoB-48-containing, cholesteryl ester-rich, smaller chylomicron remnant particles that result from lipoprotein lipase hydrolysis of large, TG-rich chylomicron particles are felt by some to be highly atherogenic [30]. It is not clear, however, whether they are more atherogenic than the apoB100-containing 'remnants' of VLDL particles; the intermediate density lipoproteins (IDL) and low density lipoproteins (LDL). Since IDL and LDL particles are far more numerous in the circulation than chylomicron remnants, it stands to reason that they will contribute *en masse* far more to the atherogenic process than apoB-48-containing particles. Furthermore, the increased apoB-48-containing particle production, which is a feature of insulin resistant states, likely aggravates the postprandial hypertriglyceridemia that characterizes these conditions, but quantitatively probably does not contribute substantially to the fasting hypertriglyceridemia of these conditions. In

summary, although overproduction of apoB-48-containing chylomicron particles in insulin resistant states has been well documented in animal models and in humans, and the mechanisms are beginning to be elucidated, it is not known how much this phenomenon contributes quantitatively to the hypertriglyceridemia or the atherogenicity of these conditions.

Why is high density lipoprotein (HDL) cholesterol content and particle number reduced in insulin resistant states?

There are numerous genetic, metabolic and inflammatory causes of low HDL, with insulin resistant states being foremost amongst them. Whole body tracer and stable isotope enrichment studies in animals and humans conducted over the past few decades have consistently shown that accelerated clearance rather than reduced production of HDL particles underlies most conditions of HDL deficiency [31]. It has also become apparent that the composition of HDL particles markedly affects its clearance from the circulation, contributing to a lowering of HDL cholesterol and, to a lesser extent, apoA-I concentrations (a surrogate of HDL particle numbers since there are two to four apoA-I molecules per HDL particle). The typical dyslipidemia of insulin resistant states (obesity, metabolic syndrome and type 2 diabetes) is characterized by hypertriglyceridemia, low HDL and small, dense LDL particles. We have shown, in a series of experiments in humans and in the New Zealand White rabbit, that the hypertriglyceridemia of insulin resistant states results in modification of HDL composition, including but not limited to triglyceride enrichment and cholesteryl ester depletion of the HDL particles, which, in the presence of the enzyme hepatic lipase, results in loss of apoA-I from the circulation and ultimately a lowering of HDL concentration [32-44]. Clearly, this is not the only mechanism for HDL lowering in these conditions but it appears to be an important pathway. In summary, the 'innocent bystander' theory of HDL lowering in insulin resistant states suggests that as a consequence of the hypertriglyceridemia, exchange of lipids and apolipoproteins between the elevated pool of TRL and HDL, altered HDL composition predisposes the HDL particle for hepatic lipase-mediated hydrolysis and clearance by liver and kidney of the resulting HDL remnants and free or lipid-poor apoA-I shed from HDL in the process of lipolysis. It is unclear, at the present time, whether low HDL is simply a marker of the atherogenic state that accompanies insulin resistance or whether low HDL is directly implicated in promoting atherogenesis by virtue of the diminished number of HDL particles in these conditions. Thus far, studies of the pharma-

ceutical modulation of HDL concentrations (primarily with Niacin and its derivatives or with CETP inhibitors) have failed to demonstrate an antiatherogenic effect of modulating HDL plasma concentrations and genetic studies have suggested that the plasma concentration of HDL does not play a primary role in atherogenesis, despite its numerous, demonstrated antiatherogenic properties. Considerable attention is now turning to the functionality of HDL and its role in macrophage-specific reverse cholesterol transport, with de-emphasis of its plasma concentrations in the process of atherogenesis.

Summary and conclusions.

We have provided a few examples of how integrative, whole body, mechanistic studies in animal models and humans can shed light on clinically important aspects of lipoprotein metabolism, with a focus on the typical dyslipidemia of insulin resistant states. Lipoprotein physiology lends itself to whole body, integrative physiological studies in view of the complex interactions between classes of lipoprotein particles in the circulation and between lipoproteins and tissues. It is also a field in which profound interspecies differences can lead to misleading or incorrect assumptions in extrapolating findings from animal models to the human. Validation of findings in a wide range of experimental model systems and in differing species, including studies in humans, is necessary to avoid the pitfalls discussed above. Employing both *in vivo* and *in vitro* experimental methods will continue to move the field ahead and expand our knowledge of the devastating metabolic consequences of overnutrition.

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List of Abbreviations

TRL	triglyceride rich lipoprotein
apoB	apolipoprotein B
TG	triglyceride
VLDL	very low-density lipoprotein
LDL	low-density lipoprotein

IDL	intermediate-density lipoprotein
HDL	high-density lipoprotein
CETP	cholesteryl ester transfer protein

References

1. Magkos,F, Patterson,B.W., and Mittendorfer,B. 2007. Reproducibility of stable isotope-labeled tracer measures of VLDL-triglyceride and VLDL-apolipoprotein B-100 kinetics. *J. Lipid Res.* **48**:1204-1211.
2. Chan,D.C., and Watts,G.F. 2011. Dyslipidaemia in the metabolic syndrome and type 2 diabetes: pathogenesis, priorities, pharmacotherapies. *Expert. Opin. Pharmacother.* **12**:13-30.
3. Lewis,G.F., Uffelman,K.D., Szeto,L.W., Weller,B., and Steiner,G. 1995. Interaction between free fatty acids and insulin in the acute control of very low density lipoprotein production in humans. *J Clin Invest* **95**:158-166.
4. Duez,H., Lamarche,B., Valero,R., Pavlic,M., Proctor,S., Xiao,C., Szeto,L., Patterson,B.W., and Lewis,G.F. 2008. Both intestinal and hepatic lipoprotein production are stimulated by an acute elevation of plasma free fatty acids in humans. *Circulation* **117**:2369-2376.
5. Xiao,C., Dash,S., Morgantini,C., and Lewis,G.F. 2013. Novel role of enteral monosaccharides in intestinal lipoprotein production in healthy humans. *Arterioscler. Thromb. Vasc. Biol.* **33**:1056-1062.
6. Lewis,G.F., Uffelman,K.D., Szeto,L.W., and Steiner,G. 1993. Effects of acute hyperinsulinemia on VLDL triglyceride and VLDL apoB production in normal weight and obese individuals. *Diabetes* **42**:833-842.
7. Pavlic,M., Xiao,C., Szeto,L., Patterson,B.W., and Lewis,G.F. 2010. Insulin acutely inhibits intestinal lipoprotein secretion in humans in part by suppressing plasma free fatty acids. *Diabetes* **59**:580-587.
8. Xiao,C., Pavlic,M., Szeto,L., Patterson,B.W., and Lewis,G.F. 2011. Effects of acute hyperglucagonemia on hepatic and intestinal lipoprotein production and clearance in healthy humans. *Diabetes* **60**:383-390.
9. Xiao,C., Bandsma,R.H., Dash,S., Szeto,L., and Lewis,G.F. 2012. Exenatide, a glucagon-like peptide-1 receptor agonist, acutely inhibits intestinal lipoprotein production in healthy humans. *Arterioscler. Thromb. Vasc. Biol.* **32**:1513-1519.
10. Adeli,K., Taghibiglou,C., Van Iderstine,S.C., and Lewis,G.F. 2001. Mechanisms of hepatic very low-density lipoprotein overproduction in insulin resistance. *Trends Cardiovasc. Med.* **11**:170-176.
11. Lewis,G.F., Carpentier,A., Adeli,K., and Giacca,A. 2002. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr. Rev.* **23**:201-229.
12. Xiao,C., and Lewis,G.F. 2012. Regulation of chylomicron production in humans. *Biochim. Biophys. Acta* **1821**:736-746.

13. Xiao,C., Hsieh,J., Adeli,K., and Lewis,G.F. 2011. Gut-liver interaction in triglyceride-rich lipoprotein metabolism. *Am. J. Physiol Endocrinol. Metab* 301:E429-E446.
14. Adeli,K., and Lewis,G.F. 2008. Intestinal lipoprotein overproduction in insulin-resistant states. *Curr. Opin. Lipidol.* 19:221-228.
15. Duez,H., Pavlic,M., and Lewis,G.F. 2008. Mechanism of intestinal lipoprotein overproduction in insulin resistant humans. *Atheroscler. Suppl* 9:33-38.
16. Taghibiglou,C., Carpentier,A., Van Iderstine,S.C., Chen,B., Rudy,D., Aiton,A., Lewis,G.F., and Adeli,K. 2000. Mechanisms of hepatic very low density lipoprotein overproduction in insulin resistance. Evidence for enhanced lipoprotein assembly, reduced intracellular apob degradation, and increased microsomal triglyceride transfer protein in a fructose-fed hamster model. *J Biol Chem* 275:8416-8425.
17. Taghibiglou,C., Rashid-Kolvear,F., Van Iderstine,S.C., Le Tien,H., Fantus,I.G., Lewis,G.F., and Adeli,K. 2002. Hepatic Very Low Density Lipoprotein-ApoB Overproduction Is Associated with Attenuated Hepatic Insulin Signaling and Overexpression of Protein-tyrosine Phosphatase 1B in a Fructose-fed Hamster Model of Insulin Resistance. *J Biol. Chem.* 277:793-803.
18. Carpentier,A., Taghibiglou,C., Leung,N., Szeto,L., Van Iderstine,S.C., Uffelman,K.D., Buckingham,R., Adeli,K., and Lewis,G.F. 2002. Ameliorated hepatic insulin resistance is associated with normalization of microsomal triglyceride transfer protein expression and reduction in very low density lipoprotein assembly and secretion in the fructose-fed hamster. *J. Biol. Chem.* 277:28795-28802.
19. Lewis,G.F., Naples,M., Uffelman,K., Leung,N., Szeto,L., and Adeli,K. 2004. Intestinal lipoprotein Production is Stimulated by an Acute Elevation of Plasma Free Fatty Acids in the Fasting state: Studies in Insulin Resistant and Insulin Sensitized Syrian Golden Hamsters. *Endocrinology* 145:5012.
20. Leung,N., Naples,M., Uffelman,K., Szeto,L., Adeli,K., and Lewis,G.F. 2004. Rosiglitazone improves intestinal lipoprotein overproduction in the fat-fed Syrian Golden hamster, an animal model of nutritionally-induced insulin resistance. *Atherosclerosis* 174:235-241.
21. Lewis,G.F., Uffelman,K., Naples,M., Szeto,L., Haidari,M., and Adeli,K. 2005. Intestinal lipoprotein overproduction, a newly recognized component of insulin resistance, is ameliorated by the insulin sensitizer rosiglitazone: studies in the fructose-fed Syrian golden hamster. *Endocrinology* 146:247-255.
22. Federico,L.M., Naples,M., Taylor,D., and Adeli,K. 2006. Intestinal insulin resistance and aberrant production of apolipoprotein B48 lipoproteins in an animal model of insulin resistance and metabolic dyslipidemia: evidence for activation of protein tyrosine phosphatase-1B, extracellular signal-related kinase, and sterol regulatory element-binding protein-1c in the fructose-fed hamster intestine. *Diabetes* 55:1316-1326.
23. Hein,G.J., Baker,C., Hsieh,J., Farr,S., and Adeli,K. 2013. GLP-1 and GLP-2 as yin and yang of intestinal lipoprotein production: evidence for predominance of GLP-2-stimulated postprandial lipemia in normal and insulin-resistant states. *Diabetes* 62:373-381.
24. Hsieh,J., Longuet,C., Baker,C.L., Qin,B., Federico,L.M., Drucker,D.J., and Adeli,K. 2010. The glucagon-like peptide 1 receptor is essential for postprandial lipoprotein synthesis and secretion in hamsters and mice. *Diabetologia* 53:552-561.
25. Hsieh,J., Longuet,C., Maida,A., Bahrami,J., Xu,E., Baker,C.L., Brubaker,P.L., Drucker,D.J., and Adeli,K. 2009. Glucagon-like peptide-2 increases intestinal lipid absorption and chylomicron production via CD36. *Gastroenterology* 137:997-1005, 1005.
26. Qin,B., Qiu,W., Avramoglu,R.K., and Adeli,K. 2007. Tumor necrosis factor-alpha induces intestinal insulin resistance and stimulates the overproduction of intestinal apolipoprotein B48-containing lipoproteins. *Diabetes* 56:450-461.
27. Haidari,M., Leung,N., Mahbub,F., Uffelman,K.D., Kohen-Avramoglu,R., Lewis,G.F., and Adeli,K. 2002. Fasting and postprandial overproduction of intestinally derived lipoproteins in an animal model of insulin resistance. Evidence that chronic fructose feeding in the hamster is accompanied by enhanced intestinal de novo lipogenesis and ApoB48-containing lipoprotein overproduction. *J. Biol. Chem.* 277:31646-31655.
28. Duez,H., Lamarche,B., Uffelman,K.D., Valero,R., Cohn,J.S., and Lewis,G.F. 2006. Hyperinsulinemia is associated with increased production rate of intestinal apolipoprotein B-48-containing lipoproteins in humans. *Arterioscler. Thromb. Vasc. Biol.* 26:1357-1363.
29. Campos,H., Khoo,C., and Sacks,F.M. 2005. Diurnal and acute patterns of postprandial apolipoprotein B-48 in VLDL, IDL, and LDL from normolipidemic humans. *Atherosclerosis* 181:345-351.
30. Proctor,S.D., Vine,D.F., and Mamo,J.C. 2002. Arterial retention of apolipoprotein B(48)- and B(100)-containing lipoproteins in atherogenesis. *Curr. Opin. Lipidol.* 13:461-470.
31. Rashid,S., Patterson,B.W., and Lewis,G.F. 2006. Thematic review series: Patient-Oriented Research. What have we learned about HDL metabolism from kinetics studies in humans? *J. Lipid Res.* 47:1631-1642.
32. Lamarche,B., Rashid,S., and Lewis,G.F. 1999. HDL metabolism in hypertriglyceridemic states: an overview. *Clin. Chim. Acta* 286:145-161.
33. Lamarche,B., Uffelman,K.D., Carpentier,A., Cohn,J.S., Steiner,G., Barrett,P.H., and Lewis,G.F. 1999. Triglyceride enrichment of HDL enhances in vivo metabolic clearance of HDL apo A-I in healthy men. *J. Clin. Invest* 103:1191-1199.
34. Lamarche,B., Uffelman,K.D., Steiner,G., Barrett,P.H., and Lewis,G.F. 1998. Analysis of particle size and lipid composition as determinants of the metabolic clearance of human high density lipoproteins in a rabbit model. *J. Lipid Res.* 39:1162-1172.

35. Lewis,G.F., Lamarche,B., Uffelman,K.D., Heatherington,A.C., Szeto,L.W., Honig,M.A., and Barrett,H.R. 1997. Clearance of postprandial and lipolytically-modified human HDL in rabbits and rats. *J Lipid Res* **38**:1771-1781.
36. Lewis,G.F., Uffelman,K.D., Lamarche,B., Cabana,V.G., and Getz,G.S. 1998. Production of small HDL particles after stimulation of *in vivo* lipolysis in hypertriglyceridemic individuals. Studies before and after triglyceride-lowering therapy. *Metabolism* **47**:234-242.
37. Lewis,G.F., Murdoch,S., Uffelman,K., Naples,M., Szeto,L., Albers,A., Adeli,K., and Brunzell,J.D. 2004. Hepatic lipase mRNA, protein and plasma enzyme activity is increased in the insulin-resistant fructose-fed Syrian Golden hamster and is partially normalized by the insulin sensitizer, rosiglitazone. *Diabetes* **53**:2893-2900.
38. Rashid,S., Uffelman,K.D., Barrett,P.H.R., Vicini,P., Adeli,K., and Lewis,G.F. 2001. Triglyceride enrichment of HDL does not alter selective cholesteryl ester clearance in rabbits. *J Lipid Res* **42**:265-271.
39. Rashid,S., Barrett,P.H., Uffelman,K.D., Watanabe,T., Adeli,K., and Lewis,G.F. 2002. Lipolytically modified triglyceride-enriched HDLs are rapidly cleared from the circulation. *Arterioscler. Thromb. Vasc. Biol.* **22**:483-487.
40. Rashid,S., Uffelman,K.D., and Lewis,G.F. 2002. The mechanism of HDL lowering in hypertriglyceridemic, insulin-resistant states. *J Diabetes Complications* **16**:24-28.
41. Rashid,S., Watanabe,T., Sakaue,T., and Lewis,G.F. 2003. Mechanisms of HDL lowering in insulin resistant, hypertriglyceridemic states: the combined effect of HDL triglyceride enrichment and elevated hepatic lipase activity. *Clin. Biochem.* **36**:421-429.
42. Rashid,S., Trinh,D.K., Uffelman,K.D., Cohn,J.S., Rader,D.J., and Lewis,G.F. 2003. Expression of human hepatic lipase in the rabbit model preferentially enhances the clearance of triglyceride-enriched versus native high-density lipoprotein apolipoprotein A-I. *Circulation* **107**:3066-3072.
43. Xiao,C., Watanabe,T., Zhang,Y., Trigatti,B., Szeto,L., Connelly,P.W., Marcovina,S., Vaisar,T., Heinecke,J.W., and Lewis,G.F. 2008. Enhanced cellular uptake of remnant high-density lipoprotein particles: a mechanism for high-density lipoprotein lowering in insulin resistance and hypertriglyceridemia. *Circ. Res.* **103**:159-166.
44. Lewis,G.F., and Rader,D.J. 2005. New insights into the regulation of HDL metabolism and reverse cholesterol transport. *Circ. Res.* **96**:1221-1232.