CHOLESTEROL BASICS *by Ann Gerhardt, MD*

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Written by Ann Gerhardt, MD

Cholesterol travels through the bloodstream inside little balls of fat and protein called lipoproteins. I'll call them particles. We name the particles LDL, HDL and VLDL, and distinguish them from each other by the proteins, fats and cholesterol they contain.

Imagine these particles as party cheese balls, with a variety of cheeses crammed together inside a coating of chopped nuts. The cheeses are lipids – cholesterol, cholesterol esters and triglycerides (fat). The nuts are proteins and phospholipids, which do the 'work' of the particles: They enable the particles to attach to cells, transfer cholesterol and fat to and from various other particles and reverse oxidation of lipids to make them less inflammatory.

The blood levels we measure are cholesterol and fat, not number or mass of particles. An ideal *total* cholesterol is <180 mg/dl. The total cholesterol is the sum of the cholesterol in all the particles. An ideal LDL-cholesterol is < 80, HDL-cholesterol is > 45 in men and 55 in women and VLDL-cholesterol is <20. An *ideal* triglyceride level is < 75, though "normal" in the U.S. is generally given as < 150 mg/dl. VLDL particles carry most of the triglycerides.

People talk about 'good' and 'bad' cholesterol, but cholesterol is just cholesterol. If it serves as a main ingredient to make hormones or as a component of cell membranes, it is good. If it becomes oxidized and trapped in blood vessel walls, it clogs arteries and is bad. The good or bad fate of cholesterol depends on the company it keeps - what type of particle carries it and which proteins modify it.

We call LDL particles (L for lousy) 'bad' because they tend to get lodged in blood vessel walls and promote inflammation and heart attacks. Put VLDL in the 'bad' category also. HDL (H for happy) is the 'good' particle because it pulls fat and cholesterol out of LDL and blood vessel walls, then neutralizes and converts them to forms that can be disposed of.

Since the particles and their proteins, not the cholesterol content, determine the fate of cholesterol and our health, it would be useful to know their levels. Currently we can't measure the number of HDL or LDL particles, or truly assess how well they are working. Specialized laboratories measure a few of the HDL and LDL proteins, but even these numbers don't give us the whole picture. Measuring just the cholesterol content must suffice. Few people even distinguish between particles and cholesterol: We just say, "My LDL is 135", even though we mean the LDL-cholesterol is 135.

The various particles interact with each other and with the body's cells. Investigators like to say that HDL particles clear cholesterol out of the body by dumping it into the liver, but we actually know very little about how that is accomplished. Try as we might, we have yet to find what they call 'putative receptors' that clear whole HDL particles from the blood. The liver does have scavenger receptors that extract cholesterol from HDL particles and release the HDL particle back into the circulation.

The liver also pulls LDL-cholesterol from blood via LDL receptors. Even though the LDL receptor was identified first, somehow HDL got the reputation as being responsible for cholesterol transport to the liver. I'm still scratching my head over that one.

LDL-cholesterol trapped in inflamed artery walls becomes oxidized. Oxidized cholesterol stimulates further inflammation and the artery becomes progressively more inflamed, scarred and narrowed until it closes off and causes a heart attack. One of HDL's proteins, LCAT, pulls cholesterol out of LDL and blood vessel walls, converts it to the healthier ester form and incorporates it into HDL.

Under usual circumstances, HDL's proteins un-do LDL-cholesterol oxidation, thereby interrupting the atherosclerotic process and contributing to the body's anti-oxidant and anti-inflammatory defense system. This is good, but HDL doesn't always act positively. HDL's lose their anti-inflammatory activity when the body is physically stressed, as in severe infection. Under such circumstances, HDL might even contribute to inflammation.

A study of heart attack victims with normal cholesterol levels showed that even very high HDL-cholesterol levels were *not* protective or anti-inflammatory. For some reason their HDL contained lipid hydroperoxides which are pro-inflammatory. This is a perfect example of the HDL-cholesterol level not revealing how well HDL works.

Normally the body's tissues extract VLDL's triglycerides to burn for energy. Another disposal mechanism for triglycerides is CETP. One of HDL's proteins, it moves cholesterol-ester from HDL to VLDL in exchange for triglyceride. Another protein, hepatic lipase, then removes triglyceride from HDL. People with high triglycerides tend to have low HDL-cholesterol levels and more heart disease. CETP lowers VLDL triglyceride, which is good. It enriches HDL with triglyceride, which seems to be good, because 'fluffy' HDL's that contain more triglyceride than usual are associated with less heart disease. But CETP, if acting

alone, leaves the HDL depleted of cholesterol, which dogma says is bad.

My theories: The key to good cholesterol metabolism is a proper balance between CETP's action, mechanisms that load HDL with cholesterol ester and how well the LDL receptor works. Perhaps one of HDL's major and unappreciated functions is triglyceride disposal. Maybe HDL's major effect on cholesterol isn't so much to dispose of cholesterol, but to clean it up and shove it back out into the blood in a healthier form.