

and Pine Island Glacier in Antarctica, the two glaciers with the earliest recorded accelerations, are among the deepest outlets with grounding lines over 1000 m below sea level. It is likely that the large outlet glaciers such as these have eroded deeper basins than the smaller adjacent glaciers that have accelerated more recently.

In this context, a key characteristic of troughs eroded by tidewater glaciers is that they end with a shallower terminal moraine at the site of their maximum glacial cycle extent. In warmer climates, they retreat from this advanced position, leaving this moraine, or sill, as a barrier that prevents deeper water seaward of the sill from reaching the deep grounding line (see the figure). Once breached, however, the warm, salty water will sink in the cold, fresh water behind the sill and reach ice at the grounding line. Increased pressure at these greater depths lowers the melting point of this ice, increasing the melting efficiency of the warmer water. Rapid melting results. This process has been modeled for the observed sill geometry in front of and beneath Pine Island Glacier (18).

Surface meltwater cannot explain this common behavior. Penetration of surface meltwater to the glacial bed in Greenland can lead to seasonal flow acceleration (19), but the annually averaged increase in speed is only a few percent. In the case of Helheim Glacier, the relative inten-

sities of warm summers were not associated with the observed changes in glacier speed (20). And surface melting is uncommon for any of the Antarctic glaciers cited here.

Outlet glacier acceleration will probably continue. As sea ice growth and decay diminish, warmer waters will reach shallower depths and access shallower tidewater glaciers, as well as move northward along Greenland's coasts. This will lead to increasing discharge of grounded ice and accelerating sea level rise. Increased discharge could encourage longer ice shelves, helping to protect the grounding lines, but this has not been observed because ice shelves have failed to grow in front of accelerating glaciers and retreat is exceeding historical bounds. Retreating glaciers lengthen the distance warmer water must travel from any sill to the grounding line, and eventually tidewater glaciers retreat to beds above sea level. This might limit the retreat in Greenland but will save neither West Antarctica, nor the equally large subglacial basin in East Antarctica where submarine beds extend to the center of the ice sheet.

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BIOMEDICINE

Lowering LDL—Not Only How Low, But How Long?

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The causal relation between plasma low-density lipoprotein (LDL) cholesterol (LDL-C) levels and coronary heart disease is well established. Compelling evidence from between-country comparisons shows that large and lifelong diet-related differences in LDL-C levels are associated with 10-fold differences in coronary mortality (1) (see the figure). Strong support comes from observations on genetic diseases such as heterozygous familial hypercholesterolemia, in which mutations in the LDL receptor gene double LDL-C levels throughout life and increase the risk of early heart attack by more than 10-fold (2). So, it has been somewhat disappointing that treatment with cholesterol-lowering statins for 5 years

reduces the incidence of heart attacks by only 40%, even when LDL-C concentration is reduced by 80 mg/dl (3), a reduction that should give much more protection based on the population studies. A likely explanation is provided by Cohen, Hobbs, and their colleagues in this week's issue of the *New England Journal of Medicine* (4). In lowering LDL levels, the appropriate consideration may be not only how low, but also how long.

Cohen *et al.* studied middle-aged Americans with lifelong low LDL levels, owing to loss-of-function mutations in the gene encoding PCSK9, a secreted enzyme of the serine protease family. In a small number of subjects with severe nonsense mutations, the concentration of LDL-C was reduced by 38 mg/dl, and the prevalence of coronary heart disease declined by a remarkable 88%. In a larger number of subjects with a less severe missense mutation, LDL-C concentration was reduced by only 21 mg/dl, yet coronary heart disease incidence declined by 47%.

People with a mutation in a proteolytic enzyme are at a substantially lower risk for coronary heart disease because of their lifelong reduction of plasma low-density lipoprotein.

What is the function of PCSK9, and how do mutations in the *PCSK9* gene lower the concentration of LDL? Experiments in mice showed that overproduction of PCSK9 in liver and cultured hepatocytes severely reduces the number of LDL receptors (5, 6). The simplest hypothesis is that PCSK9 directly catalyzes the breakdown of LDL receptors, but this has not been demonstrated experimentally. Inasmuch as LDL receptors mediate high-efficiency removal of LDL from plasma, a reduction in the number of LDL receptors causes LDL to accumulate. Ablation of the *PCSK9* gene in mice through gene-knockout technology increased the number of LDL receptors in liver and enhanced the clearance of LDL from the plasma (7). This striking finding indicates that PCSK9 functions tonically in mice to keep LDL receptor number lower and plasma LDL concentration higher than they would be otherwise.

PCSK9 appears to have the same effect on LDL in humans. A role for PCSK9 was first rec-

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