hematopoietic cells (*5*, *6*) and indeed, cells lacking *Abca1* and *Abcg1* had an increase in lipid rafts due to accumulated cholesterol. Addition of HDL to cells lacking these ABC transporters reversed the increase in lipid rafts when cholesterol was mobilized (perhaps by alternative efflux mechanisms that are not yet fully understood) from cell membranes to HDL particles.

Patients with myeloproliferative diseases display an expansion of myeloid precursor cells and enlarged spleens and livers due to infiltration of myeloid cells. Yvan-Charvet *et al*. observed this phenotype in the $Abca1^{-/-}$ $Abcg1^{-/-}$ mice and in wild-type mice whose bone marrow was replaced with that transplanted from $Abca1^{-/-}$ $Abcg1^{-/-}$ mice. To determine if this condition could be reversed if cholesterol efflux was promoted, Yvan-Charvet *et al*. transplanted bone marrow from $Abca1^{-/-}$ $Abcg1^{-/-}$ mice into recipients that were engineered to produce high amounts of the HDL protein apolipoprotein A-1 (apoA-1). The myeloproliferative disorder was not observed, suggesting that cholesterol efflux through ABC transporters to HDL controls myeloid cell proliferation.

These experiments point to a cholesterol dependent mechanism for controlling receptor function. As hematopoietic growth factor receptors in stem cells organize in membrane rafts, the availability of cholesterol for raft formation modulates receptor function. Membrane cholesterol can come either from lipoprotein uptake or local synthesis in the cell and is balanced by elimination of cholesterol from the cell. This balance depends on ABCA1 and ABCG1 transporters that mobilize cholesterol from the membrane, and on HDL particles that act as cholesterol acceptors. Lack of ABCA1 and ABCG1 results in increased raft formation, whereas addition of HDL reduces rafts. Increased raft formation helps to cluster receptors for IL-3 and GM-CSF, leading to increased responsiveness to these hematopoietic growth factors and to increased proliferation of myeloid precursor cells.

Myeloproliferative neoplasms are potentially life-threatening conditions that include chronic myeloid leukemia, primary myelofibrosis, polycythemia vera (excess blood cells), and essential thrombocythemia (excess platelets). Myeloid precursor proliferation is usually increased in these conditions. Although imatinib and second-generation tyrosine kinase inhibitors, directed against the oncogenic BCR-ABL fusion protein, have revolutionized the treatment for patients with chronic myeloid leukemia, additional therapeutic approaches are needed in myeloproliferative neoplasms. Modulation of cellular cholesterol content by increasing HDL concentration could be an attractive strategy.

In atherosclerosis, leukocytosis is observed (*7*), but the reason has been unclear. The results of Yvan-Charvet *et al*. suggest that individuals with hypercholesterolemia may develop leukocytosis because of increased proliferation of myeloid progenitors in the bone marrow. Again, the cholesterol efflux pathway could be an interesting target for therapy.

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CLIMATE CHANGE

Dry Times Ahead

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The climate of the western United States could become much drier over the course of this century.

In the past decade, it has become impossible to overlook the signs of climate change in western North America. They include soaring temperatures, declining late-season snowpack, northward-shifted winter storm tracks, increasing precipitation intensity, the worst drought since measurements began, steep declines in Colorado River reservoir storage, widespread vegetation mortality, and sharp increases in the frequency of large wildfires. These shifts have taken place across a region that also saw the nation's highest population growth during the same period.

The climate changes in western North America, particularly the Southwest, have outstripped change elsewhere on the continent, save perhaps in the Arctic. In the past decade, many locations, notably in the headwaters region of the Colorado River, have been more than 1°C warmer than the 20th-century average. This warming has been the primary driver in reducing late-season snowpack and the annual flow of the Colorado River (*1*, *2*). These reductions, coupled with the most severe drought observed since 1900, have caused the biggest regional water reservoirs—Lake Powell and Lake Mead—to decline from nearly full in 1999 to about 50% full in 2004; there has been no substantial recovery since. All of these changes, as well as dramatic warming and drying elsewhere in the region and deep into Mexico, are consistent with projected anthropogenic climate change, but seem to be occurring faster than projected by the most recent national (*2*) and international (*3*) climate change assessments; this could indicate that substantially more severe warming and drying lies ahead.

The land surface of the West is also changing at a rate that is unprecedented since systematic monitoring began in the 20th century. Background tree mortality rates in western U.S. forests have increased rapidly in recent decades (*4*), and more than a million hectares of piñon pine mortality in the Southwest has been linked to a combination of record warm temperatures and drought not seen previously in the past 100 years (*5*). Moreover, the background forest mortality across western North America is accelerating, most likely as a result of climate change (*4*). Even the low-altitude Southwestern deserts are showing signs of widespread drought-induced plant mortality (*6*). A clear link with record regional warming again implicates global warming in driving what has been termed "global-change-type drought" (*5*) and unprecedented vegetation impacts. Similarly, the exceptional warming and associated snowpack declines have led to an accelerating increase in the frequency of large wildfires (*7*).

The warming and snowpack reductions can be confidently attributed to anthropogenic global warming (*1*–*3*), but the cause of the recent and ongoing drought is harder to nail down. Drought is not unusual in western North America, and much worse droughts occurred prior to the 20th century (*8*, *9*). The cause of the current drought could be natural,

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Signs of change. Recent drops in water levels in major reservoirs fed by the Colorado River, such as Lake Mead, may be a sign of things to come as climate change takes hold in western North America.

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with impacts exacerbated by the record warming (*9*). On the other hand, global warming theory and modeling has projected an increase in drought frequency (*3*).

It would be quite useful to scientists and decision-makers alike to know the extent to which the ongoing drying of the region is natural or anthropogenic. If we know the cause, it becomes much easier to assess what the future holds for western North America. According to climate models, global warming should lead to a continued progressive drying out of the region as it warms up and winter storm tracks shift north. Thus, it is both reassuring and troubling that observed recent climate change in the West matches these projections (*2*, *10*). Warming is bad enough, but when it is coupled to a continued reduction in winter snow and rainfall, the situation will only get worse (*3*, *11*).

Equally troubling is the observed high rate of recent climate change in western North America. This indicates that the West, like the Arctic, could be unusually sensitive to greenhouse gas emissions. However, the region's high rate of recent change could also be due to an unusual confluence of anthropogenic and natural processes that may or may not coincide into the future.

Either way, it is sobering to consider published projections of future Colorado River flow given continued anthropogenic climate change: All studies published thus far point to continued declines in the river's flow. Even assuming modest reductions in greenhouse gas emissions (i.e., assuming the Intergovernmental Panel on Climate Change's Special Report on Emission Scenarios' A1B scenario), the average annual flow of the Colorado could decrease by 20% by 2050 (*12*). At the same time, the risk of all Colorado reservoir storage (3 to 5 years' worth of water) drying up could increase to 3 chances in 10 (*13*). Such change would have profound implications for the southwestern cities (such as Los Angeles, San Diego, Phoenix, Salt Lake City, and Denver) and the agricultural production areas (for example, in southern California and Arizona) that depend on water from the Colorado River.

The above scenario does not take into account the possibility that projected anthropogenic change could coincide with a "megadrought." The tree-ring record shows that droughts lasting decades have routinely gripped western North America. The cause of these droughts lies in the oceans (*14*–*16*), but the origin of their unusual persistence remains enigmatic. As western North America currently endures its worst drought since 1900, it is important to realize that this drought might be nothing compared to what is possible in the future if megadrought and even hotter temperatures coincide.

What can be done in the face of an increasingly hot and arid western North America? Scientists and decision-makers in the West are already talking seriously about climate change adaptation strategies, particularly with respect to water resources and ecosystems management, and efforts to develop such strategies may be essential to the sustainability of the region. Both climate change and natural megadrought would likely force the West to adapt to less water and more widespread landscape transformation, so a "no-regrets" approach is to plan for such change. Improved climate science will enable better projections of future climate, and close partnerships with decision-makers throughout the region will enable the development of strategies to cope with the projected range of future climate change.

We know more about what might lie ahead for western North America than for many other regions in the world. This knowledge should ultimately translate into confidence in developing coping strategies. Moreover, western North America has vast potential for solar, wind, and geothermal renewable energy production. These resources could produce substantial regional economic benefits that will help offset the inevitable costs associated with adapting to, and slowing, climate change.

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