vate TLR4, resulting in different arrangements of the TIR domain in the cytoplasmic region of TLR4. The structure of MD-2 provides clues as to how this might come about. For example, one of the true surprises of the MD-2 structure is that neither of the two lysine residues that flank its hydrophobic pocket (Lys^{128} and Lys^{132}) bind the 1- or the 4-phosphate of lipid IVa, contrary to previous predictions (*9*). It may be that the same phosphates on lipid A are free to interact with TLR4 and thereby influence how the receptor undergoes conformational changes or, alternatively, forms dimers or higher-order receptor aggregates. Highly toxic forms of lipid A, which have six to eight acyl chains, must sit differently in the hydrophobic pocket of MD-2, perhaps enabling the lipid to bind more efficiently to TLR4. Depending on how many phosphates bind to TLR4, if any at all, or how tight the binding might be, the TLR4–MD-2 complex might form distinct types of signaling platforms in the cytoplasmic domains of TLR4 dimers and hence selectively recruit adapter molecules. Such speculations make it imperative that a high-resolution structure of MD-2 bound to a proinflammatory endotoxic ligand such as lipid A, as well as of MD-2 bound to the extracellular domain of TLR4, be resolved. Additional studies should focus on the selective recruitment of adapter molecules by different TLR4–MD-2 ligands. Better integrating the studies of function and structure will enable the design of new adjuvants and other drugs for the myriad of human inflammatory disorders associated with TLRs, including systemic lupus erythematosus, sepsis, and asthma.

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ATMOSPHERE

How Will the Stratosphere Affect Climate Change?

Changes in stratospheric chemistry and circulation associated with ozone recovery may affect the patterns of future climate change.

Mark P. Baldwin, Martin Dameris, Theodore G. Shepherd

The recent projections of climate change considered by the Intergovernmental Panel on Climate Change (IPCC) (*1*), which focus on the troposphere (up to 10-km altitude), are based on climate models that largely neglect the effects of the stratosphere on climate change. Yet, the stratosphere (at altitudes of 10 to 50 km) contains Earth's protective ozone layer, which affects the energy balance of the lower atmosphere. Furthermore, circulation changes in the lower stratosphere (up to 20-km altitude) affect tropospheric weather and climate, especially at high latitudes (*2*). Why is it so difficult to include stratospheric effects in IPCC projections?

In the past ~25 years, the composition of the stratosphere has changed substantially. Abundances of anthropogenic greenhouse gases (*3*) and ozone-depleting substances (*4*) have risen, while the ozone layer has thinned (see the figure). Following the successful implementation of the Montreal Protocol, which regulates production of ozone-depleting substances, the concentrations of these substances in the stratosphere have stabilized, and the severity of the ozone hole is expected to decrease over the coming decades. However, concentrations of most greenhouse gases will continue to rise.

The temperature of the stratosphere is determined by small quantities of gases that interact with the incoming solar and outgoing infrared radiation. Ozone heats the stratosphere by absorbing solar ultraviolet radiation. Greenhouse gases (including ozone and ozone-depleting substances) both absorb and emit infrared radiation and can thus either heat or cool the atmosphere, depending on the balance between absorption and emission; for each gas, this balance depends on altitude and temperature (*2*). In the case of carbon dioxide, increased abundances cause a net warming of the troposphere and a net cooling of the stratosphere.

Satellite observations confirm that the stratosphere has cooled since 1979, in response to a combination of increasing carbon dioxide and ozone depletion (*5*). In the lower stratosphere, the global-mean cooling appears to be primarily attributable to ozone depletion (*5*). However, the radiative changes in the lower stratosphere depend strongly on latitude: Ozone depletion has led to cooling outside of the tropics, especially in polar regions (*6*), whereas the direct radiative effects of ozone-depleting substances have had a substantial warming effect in the tropics (*7*).

This latitudinal dependence implies that the north-south temperature gradient and the wind structure of the lower stratosphere must also have changed. The altered winds modify the propagation of atmospheric Rossby waves (which are responsible for large-scale modulations of the jet stream) from the troposphere into the stratosphere. Such changes in stratospheric winds in turn affect weather and climate at Earth's surface.

For example, the ozone hole in the Southern Hemisphere spring has affected Antarctic surface climate (*8*). In the Northern Hemisphere, a natural oscillation of equatorial stratospheric winds with a period of roughly 2 years affects midwinter surface wind patterns over northern Europe (*9*). During winter, wind shifts in the lower stratosphere precede similar wind shifts at the surface (*10*), with substantial changes to both weather and the likelihood of extreme weather events (*11*). The mechanisms by which stratospheric circulation changes are communicated to the surface are not well understood (*12*), but any long-term changes to stratospheric winds and temperatures are likely to affect surface climate and climate variability.

The changes to temperature and circulation in the lower stratosphere over the past ~25 years seem to have been driven primarily by changes in ozone-depleting substances and ozone depletion. They can thus be ex-

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Ozone and climate. Chemical reactions on polar stratospheric clouds, such as those shown here (taken over Sweden from the NASA DC-8 on 14 January 2003), lead to stratospheric ozone depletion. Models predict that the ozone hole will recover over the course of this century, affecting climate patterns in the stratosphere and at Earth's surface.

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pected to reverse as the ozone layer recovers. This reversal may obscure, or even alter, the climate-change signal from other greenhouse gases. Therefore, studies attempting to explain and predict climate change must account for the combined effects of climate change and ozone recovery.

The coupled atmosphere-ocean climate models that are used to understand past and future climate change generally do not have substantial interactive chemistry or even well-represented stratospheres. These models often include the radiative effects of ozone-depleting substances and of ozone depletion, but they are not designed to predict changes to the ozone layer or the dynamics of stratosphere/troposphere coupling. Many of the models considered in the recent IPCC report (*1*) held stratospheric ozone forcing constant during the 21st century. In any case, without a well-represented stratosphere, it is unlikely that the dynamical response to stratospheric radiative changes can be captured.

Coupled chemistry-climate models, such as those used in (*5*), include good representations of the stratosphere and interactive ozone chemistry and can therefore simulate changes to the ozone layer and their coupling to climate change. According to these models, ozone recovery will not be a simple reversal of ozone depletion. Rather, the stratospheric cooling from increasing greenhouse gases will accelerate the recovery of the ozone layer, so that pre-1980 ozone abundances are expected to be reached in the middle of this century. The main reason for this acceleration is that most ozone-destroying chemical reactions will be slowed as the stratosphere cools. Beyond 2050, the ozone layer is predicted to become thicker than observed at any time in the last century as the stratosphere continues to cool.

Nearly all climate models with well-represented stratospheres indicate that the large-scale equator-to-pole overturning circulation, called the Brewer-Dobson circulation (*13*), will accelerate under climate change (*14*). This would lead to weaker westerly winds and higher temperatures in the extratropics during winter and spring. Such circulation changes would be expected to couple downward to affect surface weather, especially over the Arctic and Europe. However, stratospheric models have so far used prescribed ocean-surface temperatures, which strongly damp any tropospheric response to stratospheric changes.

Inclusion of stratospheric ozone-climate effects in coupled atmosphere-ocean climate models will not significantly alter the overall estimates of globally averaged surface warming. However, because of the possibility of dynamical responses to the stratospheric changes, projections of the evolution of polar climate could be substantially different, especially in the winter and spring in the Northern Hemisphere and spring and summer in the Southern Hemisphere. Estimates of the future evolution of rainfall and storms in northern mid-latitudes could also change.

Predicting the future effects of stratospheric change on surface climate is a substantial task. Doing so will require models that combine the coupled oceans of the current climate-prediction models with the detailed stratospheric radiation and chemistry of chemistry-climate models. This modeling was impractical for the 2007 IPCC report. It is an impending challenge for modelers to include a full representation of stratospheric circulation and chemistry in the climate simulations for the next IPCC report.

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