NSCs injected into early chick or mouse embryos are able to make a wide range of nonneuronal cell types, showing that they have the innate capacity for transdifferentiation when exposed to appropriate developmental signals (*9*).

Differences in the injury environments of salamanders and mammals suggest a strategy for understanding the biology of regeneration that will contribute to progress in regenerative medicine. The strategy is to compare and contrast the patterns of gene activity in regeneration-competent versus regeneration-deficient tissues to define which molecular signals and injury products determine whether regeneration rather than scar formation takes place. Several types of comparative models are useful: regenerating versus nonregenerating species, for example, salamanders versus frogs; regeneration-competent versus regeneration-deficient stages of the life cycle, such as frog tadpoles versus froglets; or mutant versus normal tissues, for example, the ear and heart tissue of wild-type versus MRL mutant mice (*10*). The data obtained can then be used to design molecular "cocktails" of genes or proteins that mimic an injury environment permissive for regeneration by the body's own tissues. The feasibility of this approach is indicated by the fact that mammalian muscle cells can be induced to dedifferentiate by newt limb regeneration blastema extracts (*11*). Although stem cell transplantation is likely to be the first therapeutic wave of regenerative medicine, the ability to induce regeneration of new tissues from our own cells will not be far behind.

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PERSPECTIVES: ECOLOGY

Looking Beneath the Surface

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It is widely accepted that the release of greenhouse gases into the atmosphere will have profound impacts on Earth's climate, including global warming, altered precipitation patterns, and increased storm intensities (*1*). The likely ecological impact of global change is typically assessed in experiments conducted in various ecosystems subjected to one or at most two such environmental changes. The paucity of multiple-factor, multiple-year global change studies limits our understanding of how ecosystem processes will respond to global climate change.

On page 1987 of this issue, Shaw *et al.* (*2*) take an important step toward a more integrated approach to understanding multiple global changes. The study raises questions about our ability to design and interpret studies for understanding long-term ecosystem responses to global change.

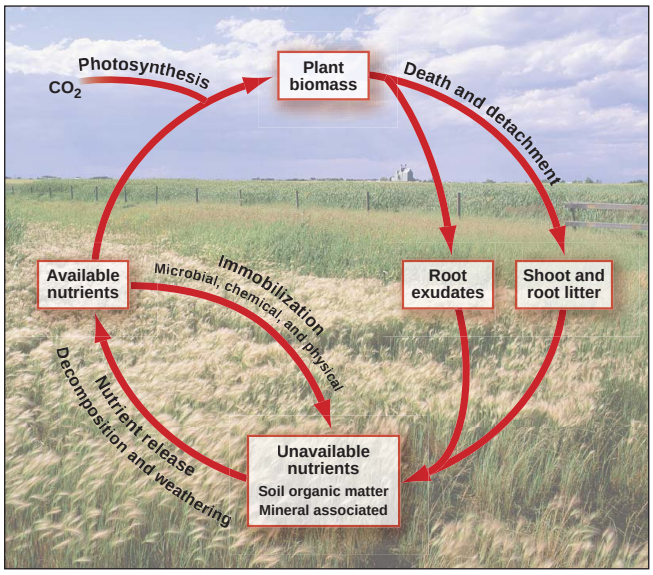
The authors report that simulated global changes—warming, increased precipitation, and increased nitrogen deposition—all increased net primary productivity (NPP) of a California annual grassland, but that elevated CO_2 reduced these global change enhancements in the third year of this field study. These findings are in sharp contrast to many earlier studies and to other findings presented in their report (*2*), which indicate that rising atmospheric CO_2 will either enhance production in grasslands or have minimal or no effects on production (*3, 4*).

Photosynthesis of almost all grass species is stimulated in the short term by increasing atmospheric CO_2 concentrations (*3*), suggesting that the potential exists for productivity responses of most grasses to increased CO_2. However, this potential is often unrealized or declines over time because of plant metabolic adjustments that optimize resource use (*4*), or because the soil cannot keep pace with the greater demand for soil nutrients by faster growing CO_2-enriched plants.

Longer term adjustments to CO_2 involve changes in soil nutrient cycling, which may further modulate plant responses. Under CO_2 enrichment, greater amounts of carbon may enter the soil organic pools, either as litter or root exudates, and may fuel microbial growth and demand for soil nutrients. This, in turn, can immobilize soil nutrients, making them less available to plants, and can reduce or eliminate a plant's ability to respond to CO_2.

But can it lead to lower productivity? The answer is, apparently, yes. Shaw *et al.* (*2*) are not the first to report CO_2-induced reductions in plant productivity. Although rare, inhibition of plant growth by elevated CO_2 has also been observed by others (*5*–*7*). Further, periods of reduced production under elevated CO_2 have been predicted in plant simulation models that incorporate soil feedback mechanisms (*8*).

Microbial immobilization of nitrogen is a common feature in many CO_2 enrichment studies (*9*) and is probably involved in some of the negative growth responses to CO_2. Elevated CO_2 inhibited NPP in the California grassland only under favorable growth conditions. Such conditions of high plant growth often deplete the soil of one or



Complex feedbacks. Litter from decaying plants and root exudates enters a large, diverse pool of nutrients that are unavailable to plants until they have been decomposed by microbes. Weathering also releases small amounts of nutrients over long time scales. Some of the available nutrients become immobilized by microbial growth; others may be rendered chemically or physically unavailable. The balance between nutrient release and immobilization determines the level of nutrients available to the plant, and hence the ultimate plant response. Increases in atmospheric CO_2 may initially stimulate photosynthesis and plant production, but soil nutrient feedbacks may constrain or eliminate that response. The long-term consequences of global change on these interactive processes are poorly understood and are likely to vary among ecosystems.

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more essential nutrients, which can eventually limit the growth response. A high-CO_2 environment could have exacerbated this growth-induced nutrient limitation, resulting in the negative NPP response (*2*).

The long-term response of nutrient-limited ecosystems to elevated CO_2 depends on the balance between processes that temporarily immobilize plant nutrients and those that release nutrients back into forms available to plants (see the figure). Decades or even centuries may be required for some of these processes to equilibrate after system perturbations such as those that are simulated in global change studies. Short-term, transient responses observed in experiments may thus not reflect the long-term, equilibrium response (*5, 8*).

This observation underscores a related problem for global change studies, especially studies that incorporate complex interactions between multiple variables: How does one interpret transient responses in light of the long time scales of many of the belowground processes? And how can information obtained by observing step changes in environmental factors—for example, an instantaneous doubling of the CO_2 concentration—be used to predict ecosystem responses in the real world of long-term, incremental changes in Earth's climate and atmospheric trace gas concentrations?

Answering both of these questions requires well-integrated computer modeling and observational investigations. Field studies, even ones that consider multiple factors, are insufficient for understanding the complex feedback responses that occur beneath the soil surface and determine the long-term system responses to global change (*8, 9*). Greater efforts must be made to understand the dynamics of nutrient cycles and to design experiments that target critical knowledge gaps. The results can then be incorporated into models to evaluate long-term consequences of incremental global changes.

Such integrated approaches in global change research are even rarer than the negative CO_2 production responses reported by Shaw *et al.* (*2*). But they will be required if we hope to achieve some predictive capability long before the results of our worldwide global change experiment materialize across the planet.

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PERSPECTIVES: CHEMISTRY

The Simplest "Enzyme"

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How small can a highly active and stereoselective catalyst be? And what are the minimal functional and structural features required in a chiral catalyst? A series of recent reports on proline-catalyzed asymmetric reactions may be pointing to the ultimate answer to these practically and fundamentally important questions. The studies are all the more significant because they address some of the most challenging and useful reactions in organic chemistry.

Asymmetric synthesis is dedicated to the preparation of handed (chiral) compounds with defined three-dimensional molecular structure (stereochemistry). The importance of stereochemistry in chemical interactions is probably best appreciated in the context of drug-receptor interactions, because most biological targets are chiral entities. Hence, there is enormous pressure to devise viable and practical methods for preparing chiral compounds in pure form.

Nature is the principal practitioner of asymmetric synthesis. Living systems use enzymes to catalyze stereoselective reactions with very high fidelity. Enzymes exploit hydrogen bonding between the active site and substrate, together with nonbonded dipole-dipole, electrostatic, and steric interactions, to orient the substrate and stabilize the transition state, leading to high levels of stereoselectivity.

The challenge associated with organizing the key transition structure in a catalytic process, such that only a single enantiomer (handedness) of a chiral product is produced, appears formidable. It was therefore long assumed that complex supramolecular structures such as those found in enzymes were required for attaining high enantioselectivity. We now know, however, that synthetic small-molecule catalysts can approach and sometimes even match the enantioselectivity and reactivity characteristic of enzymes.

Since the first reports appeared in the late 1960s, a wide variety of chiral organometallic complexes have been identified as asymmetric catalysts (*1*). These catalysts not only effect useful reactions with high levels of enantioselectivity, but often do so with a wide variety of substrates. Such generality is highly unusual with enzymes. The 2001 Nobel Prize in chemistry was given to the leading figures in the field of asymmetric catalysis in recognition of these accomplishments (*2*).

In the excitement over transition metal–based catalysts, a series of reports and patents from the early 1970s describing an enantioselective transformation that employed the natural amino acid proline as the catalyst (*3*–*6*) did not receive the attention they deserved. The chemistry was not ignored by organic chemists—the so-called Wieland-Miescher ketone prepared by proline catalysis has been used more or less continuously as a synthetic building block over the past 25 years (*7*). Yet, its broader implications for asymmetric catalysis were not appreciated until recently.

Recently, List *et al.* reported the intermolecular aldol addition reaction of acetone to various aldehydes catalyzed by proline (*8*, *9*). The authors also used other ketones as the nucleophile component. Perhaps most noteworthy is the use of hydroxy acetone, which provides 1,2-diols as the aldol addition products with aldehydes with high stereoselectivity.

Proline has also been used to activate ketones and aldehydes as the nucleophilic component in various asymmetric conjugate additions and additions to imines. Most recently, MacMillan reported the use of proline to catalyze highly enantioselective cross-aldol reactions, with different aldehyde substrates serving as both donor and acceptor in efficient addition reactions (*10*). Such transformations have constituted a "Holy Grail" of sorts in the field of asymmetric catalysis because they provide operationally simple routes to useful products without generating any wasteful by-products.

The high levels of reactivity and enantioselectivity induced by proline in these reactions likely arise from a series of interactions similar to those involved in enzymatic catalysis. Proline catalysis, similar to other catalytic processes, involves organization and activation of the substrates, transition state stabilization, and product release to afford substrate turnover. In the postulated mechanism of proline-catalyzed

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