bene ligand (*11*, *12*). These are examples of transformations of a well-known allotrope into unprecedented phosphorus(0) clusters.

These molecules are not just academic curiosities. One of the obvious advantages of base-stabilized element(0) compounds, versus their known allotropes, is their greater solubility, which facilitates further chemical transformations. As an illustration, soluble, ligand-coordinated metal(0) complexes undergo chemistry that is not possible using the insoluble elemental forms of the metal (homogeneous versus heterogeneous catalysis). Moreover, this stabilization technique is not limited to element(0) compounds, as shown already for diborene, and should allow for the solubilization and subsequent chemical transformation of elementary units of large frameworks, such as the basic unit of sand, SiO_2.

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ECOLOGY

A Matter of Timing

The cues used by birds and other species to trigger reproduction determine how successfully they can respond to climate change.

Bruce E. Lyon,[1] Alexis S. Chaine,[2] David W. Winkler[3]

Climate change is causing shifts in the distribution and phenology of many plants and animals (*1*, *2*). Birds have played a key role in detecting these changes, because long-term data are available on the distribution, migration, and breeding of many species. Studies of the timing of egg laying—a key trait with extensive records dating back half a century for some species—are providing crucial insights into the mechanisms that underlie the response to climate change.

Response to climate change. A striking geographic difference in how two populations of great tits respond to climate change raises the question about the underlying mechanisms of this variation.

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Egg laying is occurring earlier in the year in a wide variety of temperate-zone birds (*1*, *3*). Evidence that climate change is directly involved comes from geographic variation in well-studied taxa, such as European populations of flycatchers (*4*). Changes in laying date are consequential because birds must time reproduction to coincide with seasonal pulses in resources. If prey advance their emergence more rapidly than birds advance their laying (*5*), decreased reproductive success and population decline may result (*6*).

Which evolutionary and behavioral mechanisms underlie these responses to climate change (*5*, *7*–*9*)? Two mechanisms in particular have been investigated: phenotypic plasticity and evolutionary response to natural selection (*8*, *9*). With phenotypic plasticity, individual females show flexibility and alter their timing of breeding when environmental conditions change. With an evolutionary response, breeding date has a strong genetic component and change occurs by a shift in the genetic makeup of the population.

Evidence to date implicates phenotypic plasticity as the driver of most change in laying date in birds (*9*), but some populations seem to show much less plasticity than others. For example, two long-term studies of the great tit (*Parus major*; see the figure) reveal striking geographic variation in phenotypic plasticity for laying date (*5*, *7*). In a 32-year study, the mean laying date for a Dutch population shifted little in response to increasingly warm spring temperatures, leaving the birds' laying date increasingly out of step with the advancing emergence of their key caterpillar food source (*5*). However, phenotypic plasticity varied among females; some responded little to annual variation in temperature while others showed more extensive responses. Moreover, the variation in plasticity is heritable, and analyses suggest that the more plastic genotypes should eventually be favored by natural selection (*5*). In contrast, a 47-year study in England found a strong adaptive response to climate change; both the birds and their caterpillar prey have shifted in unison as warm spring temperatures arrive increasingly early (*7*). The shifts in the British population appear to be explained entirely by phenotypic plasticity, and there were no detectable differences in the degree of plasticity among females (*7*).

How do the Dutch and British tits differ? Might differences in their response mechanisms explain geographic variation in plasticity more generally?

One explanation is that the birds may use different cues to trigger egg laying. Timing of egg laying in temperate-zone birds is thought to involve many cues, integrated in a tiered fashion: Day length (photoperiod) begins the process, and then supplemental cues such as food, temperature, or the phenology of other organisms can be used to fine-tune the timing of laying to year-to-year variation in spring conditions (*10*, *11*). Variation in the relative importance of different cues could explain variation in plasticity with respect to temperature among populations or even among individuals in the same population (*12*, *13*).

For example, organisms that show little or no plasticity with respect to temperature variation—like many individuals in the Dutch great tit population—may use photoperiod as their sole cue. A bird that used only photoperiod would have a consistent breeding date unaffected by variation in environmental con-

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ditions. In contrast, complete plasticity with respect to temperature, as observed in the British great tits, would result if birds relied heavily on temperature (or some strong correlate of temperature, such as the phenology of another organism) as their sole or supplemental cue. Moreover, the apparent ability of the British birds to track changes in the timing of their prey could result if both birds and prey use the same cues.

Precisely how birds assess and compile temperature is not well understood. Nonetheless, a recent study of geographic variation in the relative importance of photoperiod and temperature-related supplemental cues in great tits provides some support for the idea that variation in plasticity can be explained by the types of cues used (*13*), and it would be fruitful to further explore these links.

Knowing which cues organisms use will be necessary for predicting the long-term impacts of climate change on the timing of breeding in birds and other organisms (*12*). Scientists typically study phenotypic plasticity by analyzing a norm of reaction—that is, a statistical measure of the response of a given genotype (or individual) to variation in some environmental variable, such as temperature, measured by the researcher. However, it is critical not to confuse a norm of reaction with the organismal traits under selection (*14*). The actual traits that produce plasticity in laying date include features of the neuroendocrine system that assess and integrate environmental cues and trigger egg laying (*11*, *14*). Without experiments, it is exceedingly difficult to verify which cues are used by the organism and how they are used. At best, our investigations examine close approximations of the actual cues; at worst, we may analyze proxies that are the wrong cues.

This inaccuracy may hamper our ability to understand variation in plasticity across populations and to make predictions about how plasticity might evolve in the future. For example, say we compare laying dates in relation to temperature, but the organism actually assesses another cue that is reasonably well correlated with temperature (for example, leaf bud break in a plant species). As spring temperatures increase over time, the correlation between what we measure (temperature) and what the birds assess (plants) may change, making extrapolations from current reaction norms problematic. Geographic variation among populations—such as the British and Dutch tits—might occur not because the populations use different cues, but because the cues they use vary geographically in their correlation with temperature.

Laying date can affect offspring production, Darwinian fitness, and population stability (*6*, *15*). The widespread observation that early breeders produce more offspring than late breeders implies that time in season is a direct cause of variation in reproductive success (*15*). However, experiments show that about half of the variation in reproductive success results from differences in individual quality, independent of season (*15*).

The fact that individuals within populations vary so much in their timing of breeding implies that factors other than external cues determine the timing of breeding, a detail that is often not fully explored. Thus, a clearer understanding of all factors—including cues and individual quality—that trigger breeding would improve our understanding of not only the potential for phenotypic plasticity to cope with climate change, but also the demographic consequences of such plasticity. Only by drawing direct links between the specific cues and mechanisms used to time egg laying, the potential for microevolution in these mechanisms, and the demographic consequences of this flexibility for exploiting ever-changing food sources will we be able to predict and mitigate the effects of climate change on regional population persistence.

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PLANT SCIENCE

Using Tobacco to Treat Cancer

Charles J. Arntzen

Plant biotechnology brings us closer to personalized therapies as tobacco plants are genetically reprogrammed to produce a vaccine to treat lymphoma.

Tobacco, which has gained a reputation as a cause of cancer, may soon earn some praise rather than recrimination after being used by McCormick *et al.* to manufacture patient-specific vaccines against follicular B cell lymphoma (see the figure) (*1*).

Follicular lymphomas are a subtype of non-Hodgkin's lymphoma, the seventh leading cause of cancer-related deaths in the United States (*2*), and are a malignant disease of the lymphatic system that originates from cells of the immune system (lymphocytes). The administration of a tobacco-derived non-Hodgkin's lymphoma vaccine (a single-chain segment of an antibody protein) in a human clinical trial resulted in immune responses in more than 70% of the patients. A majority of patients showed a cellular immune response, suggesting that the vaccine specifically directs the immune system to attack cancer cells. The study not only demonstrates the safety and efficacy of the plant-made protein, but represents the first time that such responses have been observed using a subcutaneously administered antibody-based vaccine in the absence of a carrier protein (which typically boosts the immune response and has been used in all previous clinical studies). Bayer AG, a major pharmaceutical company, has acquired the supporting data from the new study, and very recently announced the opening of a production facility that will use tobacco to manufacture biopharmaceuticals, the first of which will be a candidate patient-specific antibody vaccine for non-Hodgkin's lymphoma therapy.

Although the report of McCormick *et al.* will undoubtedly be appreciated as an advance in immunotherapy for cancer patients, the results will likely generate even greater excitement in the plant biotechnology community. It has been almost two decades since genetically engineered plants were shown to produce monoclonal antibodies or vaccine subunits (the latter can be antigens that

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