laglutide for 12 weeks with the primary goal to examine smoking cessation reported reduced alcohol consumption (*14*), whereas people with alcohol use disorder randomized to exenatide once weekly for 26 weeks did not reduce the overall number of heavy-drinking days, despite exhibiting attenuated alcohol cue reactivity in the septal and ventral striatum regions of the brain, as determined by functional magnetic resonance imaging (*15*). Anecdotal reports of improvements in a wide range of dependence-related behaviors have prompted initiation of multiple randomized controlled trials to determine whether GLP-1 medicines might have therapeutic utility in these disorders.

The success of GLP-1 medicines for T2D and obesity has fostered interest in developing next-generation therapies that are even more effective and produce greater weight loss than current GLP-1R agonists. Tirzepatide simultaneously targets GIPR and GLP-1R, resulting in unprecedented glycemic control and weight loss (*1*). Like GLP-1, GIP is also a gut peptide that is important for physiological control of blood glucose, and pharmacological activation of GIPR with a long-acting GIPR agonist also produces weight loss in humans (NCT04586907). As GIP and GLP-1 exert complementary actions through distinct receptors, simultaneous activation of both receptors provides an opportunity to maximize metabolic benefits beyond targeting only one receptor. Additional GLP-1 medicines under clinical development include those that are combined with GIPR antagonists, glucagon receptor or GLP-2R agonists, or amylin receptor agonists. The goal is to achieve greater weight loss while preserving or ideally enhancing the cardiorenal and hepatic actions of current GLP-1R agonists. These new medicines are most often designed as peptides for parenteral administration, and in some cases, developed as small molecules or peptides formulated for oral administration.

How might these emerging combinations improve outcomes in people with T2D or obesity, at risk for developing cardiovascular, kidney, liver, or neurodegenerative disease? The receptors for glucagon, GIP, and amylin are all expressed within the central nervous system, but much less is known about their potential for neuroprotection, relative to GLP-1R agonism. These receptors are not highly expressed in the human heart, and their likelihood of modifying GLP-1–mediated cardioprotection has not been carefully scrutinized. Glucagon receptors are expressed in hepatocytes and kidney cells, and the available data suggest that glucagon receptor activation may confer additional benefits, perhaps reducing rates of metabolic liver disease and diabetic kid-

ney disease beyond that possible with GLP-1 alone. Although a short-acting amylin analog, pramlintide, has been approved for the treatment of diabetes in the United States for 19 years, amylin receptors are expressed predominantly in the nervous system, and there are no definitive studies examining whether amylin receptor agonism improves long-term health outcomes. A GLP-2 analog, teduglutide, has been used for more than a decade to treat intestinal failure, and GLP-2R agonism may improve gut barrier function and reduce liver inflammation. However, clinical experience with GLP-2R agonists in people with T2D or obesity, alone or in combination with GLP-1R agonists, is limited.

The initial chapter of GLP-1 innovation focused on glucose control, and later, weight loss. Subsequent waves seem likely to improve health outcomes in people with a range of chronic disorders. Dozens of new molecules are being interrogated in the clinic, with some likely to target new mechanisms and achieve greater benefits in multiple disorders beyond simply more effective glucose control and weight loss. A wide range of clinical trials is underway, with results likely to support expansion of the range of clinical indications benefiting from GLP-1 therapies. Hence, after almost two decades of the clinical use of GLP-1 for T2D and 10 years after the first GLP-1 medicine, liraglutide, was approved for weight loss in people with obesity, the next decade may bring even greater progress, introducing more powerful GLP-1 medicines while expanding the utility of GLP-1 therapeutics beyond currently established cardiometabolic disorders. ∎

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ECOLOGY

A hard fruit to swallow

Foraging niches become more specialized toward bird range limits

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Children are often taught about the natural world through facts about species, such as what a toucan eats. Yet species are not homogeneous, and different populations within a species vary in how they use their environment. Gaining a better understanding of this variation is a key challenge in ecology. One idea is that niche variation should be particularly apparent toward the edges of species' geographic distributions, where the amount or quality of habitat declines (*1*). However, there is little theory that predicts which niche components will vary toward range edges and remarkably few compelling examples from nature. On page 331 of this issue, Martins *et al.* (*2*) offer both, combining optimal foraging theory and observed foraging patterns to predict and demonstrate that fruit-eating (frugivorous) birds have narrower diet niches toward the edges of their geographic ranges. Accounting for such heterogeneity in resource use will be important for accurately predicting species' responses to environmental change (*3*, *4*).

Optimal foraging theory predicts that for a given set of environmental constraints, a population will evolve a foraging strategy (where, when, and what to eat) that maximizes fitness (*5*, *6*). Martins *et al.* argued that under environmentally stressful conditions, such as the edges of species' ranges, birds face more stringent energetic constraints and predicted that the optimal foraging strategy for frugivorous birds would be to eat the biggest fruits they can fit in their beaks. Combining large datasets on species traits, interactions, and geographic distributions, they showed that frugivorous birds do indeed maximize the match between fruit size and beak size more closely at their range edges than in their range center, resulting in a narrower

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foraging niche in range-edge populations.

One challenge in studying niche changes toward range edges is determining whether they are driven by changes in resource availability or use. Populations may use a narrower set of resources simply because the diversity of available resources declines. For example, species may have fewer food sources at their range edge (see the figure). A more interesting scenario occurs when a niche narrows owing to genetic or behavioral changes in resource use, which leads to increased specialization of edge populations. For example, a species might meet its energetic needs by using a wide variety

use "optimal" to refer both to maximum trait matching and the optimal foraging strategy, begging the question of why birds in the range center would not also forage optimally. Indeed, birds may be foraging optimally in the range center as well, even though they are not eating the largest possible fruits. For example, eating fruits of varied sizes may help them avoid competitors or predators.
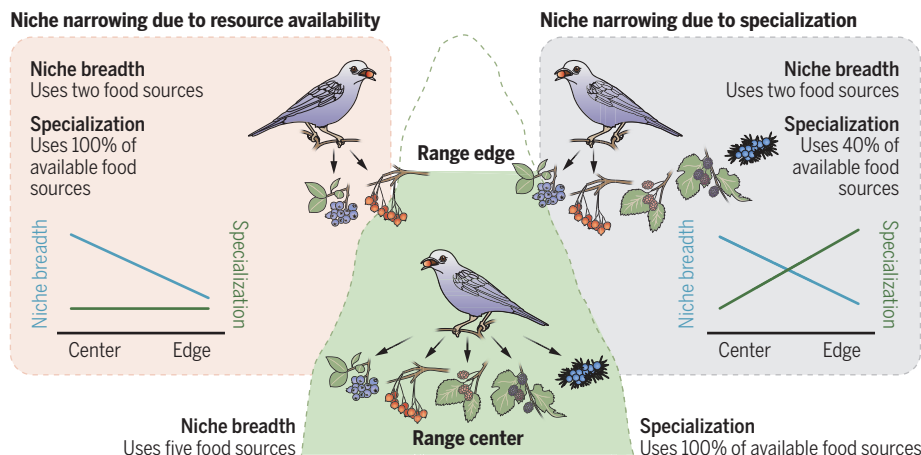
Although it seems intuitive that populations at range edges will be increasingly constrained in which resources they can use, this need not be the case. Niche breadth could expand at range edges, ow-

change toward range edges by creatively synthesizing disparate large datasets. Yet opportunistic data syntheses have important constraints. They often require simplifying assumptions. The authors assumed that some unmeasured component of the environment becomes more stressful toward range edges, which is not always the case (11). They also assumed that traits themselves, in this case beak or fruit size, do not vary substantially across populations, such that species-level means can capture local trait matching. In addition, geographic biases in data availability plague most macroecological syntheses and may conceal important variation in the patterns of, and mechanisms underlying, changes in niche breadth. Overcoming these limitations requires targeted data collection on species interactions and traits across large spatial scales. The burden of targeted data collection can be lessened through distributed experiments and observation networks using standardized protocols (12, 13), which also strengthen international collaboration, exchange, and benefit sharing.

Targeted measurements of spatial variation in niche breadth and species interactions are especially important as ecologists strive to better forecast species' responses to global change. If niche breadth and resource use commonly change across species' ranges, it will be more difficult to accurately predict local trophic interactions based on species-level trait matching, or the impact of changing resources based on species-level interaction networks (4). More broadly, population differences might contribute to the unpredictability of species' local responses to climate change (14, 15). Ultimately, a "one-size-fits-all" approach might not be appropriate to capture ecological functioning, which calls for more a nuanced consideration of ecologically relevant variation among populations across species' ranges. ■

Niche breadth narrows toward a species' range edge

In populations that live closer to the range edge, niche breadth—for example, the diversity of food resources a species uses (arrows)—can narrow owing to either reduced diversity of resources available (left) or increased specialization, such that with the same diversity of resources available, a species uses a narrower subset of them (right). Martins *et al.* show that range-edge populations of frugivorous birds specialize on fruits that match their beak size.

Niche narrowing due to resource availability

Niche breadth
Uses two food sources

Specialization
Uses 100% of available food sources

Niche breadth / Specialization (Center — Edge)

Range edge

Niche breadth
Uses five food sources

Range center

Niche narrowing due to specialization

Niche breadth
Uses two food sources

Specialization
Uses 40% of available food sources

Niche breadth / Specialization (Center — Edge)

Specialization
Uses 100% of available food sources

of foods under mild conditions in its range center but only be able to meet them by using the best-quality foods under energetically stressful conditions at its range edge. Martins *et al.* teased these scenarios apart in a compelling manner by measuring how birds use fruit relative to fruit availability. They found that birds have diverse fruit sizes available throughout their ranges but use a narrower subset of available fruits at the range edge, demonstrating that niche narrowing results from greater behavioral specialization.

Optimal foraging theory predicts that all populations will maximize their foraging efficiency but that the optimal strategy for doing so will vary among environments (7). The optimal resource itself may be context dependent, for example, if there is no single "best" food source across sites for a given species but rather the optimal food depends on the energetic or nutrient requirements at a given site. A potential point of confusion is that Martins *et al.*

ing to increased environmental opportunity (e.g., greater diversity of potential food sources) or increased generalization (e.g., use of a greater proportion of available foods). Indeed, some animals use a greater breadth of resources toward their range edges owing to a lower availability of preferred foods (8) or legacy effects of past range expansion (9). Further, although Martins *et al.* predicted that food choice changes to compensate for some unspecified environmental stress, many range limits are imposed by a lack of food itself (10). Thus, foraging could be the niche component that becomes more stressful toward range edges. It is not known whether or how niche breadth generally changes toward range edges or which niche components are most likely to change. The answer likely depends on the species, its degree of resource or habitat specialization, and environmental and historical contexts.

Martins *et al.* provide a rare example of how niche breadth and specialization

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