PERSPECTIVES: ECOLOGY

Incredible Journeys

Keith A. Hobson

The most baffling and complex phenomena in nature are sometimes unraveled by the simplest experiments. Tracking the migrations of different populations of a particular mammal or bird over vast geographical ranges and calculating whether the populations intermix has proven intractable for all but the most conspicuous of species. For migratory birds that breed annually in North America and Europe and migrate to more southerly wintering grounds, conventional marking methods are woefully inadequate for deciphering the mystery of their movements. The task is even more formidable for very small organisms such as migratory insects.

Across continents, there are often predictable patterns in the abundance of naturally occurring stable isotopes such as carbon (^{13}C), hydrogen (^{2}H deuterium), sulfur (^{34}S), and strontium (^{87}Sr). Of particular value is the abundance of ^{2}H in rainfall, which has a characteristic latitudinal and continental distribution (see the figure). ^{2}H is taken up by birds in their food and water and becomes deposited in feathers and other metabolically inactive tissues. Most migratory birds grow new feathers before migration. Thus, the approximate latitude at which a bird's migration started can be readily calculated by measuring the ratio of ^{2}H to normal hydrogen in a single feather. As exemplified by the Rubenstein *et al.* report (*1*) on page 1062 of this issue, this approach enables delineation of large-scale population structures in small migratory animal populations.

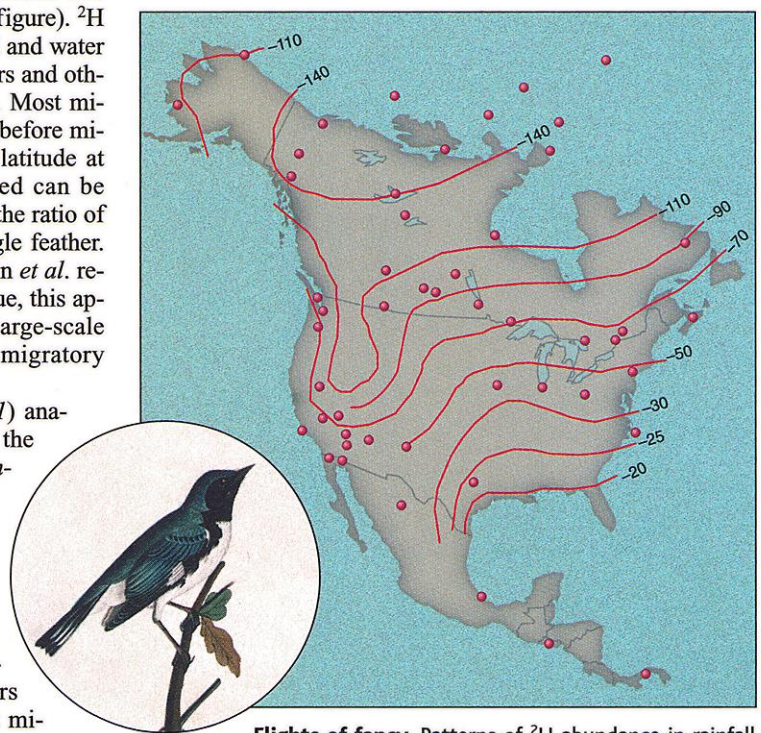
Rubenstein and colleagues (*1*) analyzed the migration patterns of the black-throated blue warbler (*Dendroica caerulescens*). Capitalizing on natural patterns of ^{2}H and ^{13}C abundance throughout the warbler's breeding range and measuring isotope ratios for ^{2}H and ^{13}C in feathers, they reveal the astonishing fact that two distinct subpopulations of warblers exist, with completely different migratory strategies. Warblers wintering in the western Caribbean islands migrate from the northern United States, whereas those wintering in the eastern Caribbean islands arrive from the southern United States.

The author is with the Canadian Wildlife Service, Saskatoon, Saskatchewan S7N 0X4, Canada. E-mail: keith.hobson@ec.gc.ca

Continental distribution patterns of isotopes in rainfall were established decades ago by isotope hydrologists. Indeed, botanists have spent years analyzing patterns of ^{13}C distribution in plants resulting from climatic, altitudinal, and photosynthetic factors. Cormie and colleagues (*2*) were among the first to show that continental patterns of isotopes in rainfall pass from surface waters into plants and ultimately into herbivores. Given that insectivorous birds are a step above herbivores in the food chain, it comes as no surprise to find that rainfall isotope signatures are also present in birds' feathers. This discovery has prompted a major breakthrough in avian migration tracking (*3*). In contrast to traditional capture-recovery methods, isotope tracking only requires knowledge of the distribution of isotope abundance across the geographical range of the target organism. Hence, every isotope measurement after capture becomes a recapture because, like bands, rings, or other markers, the target organism's tissues contain information about its place of origin. With this strategy, investigators are freed from the "needle in a haystack" dilemma of trying to recover banded individuals at stopover locations or on remote wintering grounds.

Several recent studies have used ^{2}H rainfall distribution patterns to calculate the interactions of migratory populations and to investigate population structure in species ranging from monarch butterflies (*Danaus plexippus*) (*4*) to Cooper's hawks (*Accipiter cooperii*) (*5*). With this approach, Kelly *et al.* (*6*) reported the surprising finding that the Wilson's warbler (*Wilsonia pusilla*) migrates from North America to Central America in a leapfrog pattern, such that more northerly breeding populations fly over more southerly breeding populations to reach wintering grounds that are much farther south. Rubenstein *et al.* (*1*) aptly demonstrate that surprising migrations would never be revealed with conventional mark-and-recapture methods. They also report a longitudinal gradient in ^{13}C in the feathers of the black-throated blue warbler across the northern part of its breeding range. Similarly, the origins of wintering monarch butterflies have been determined by combining data on natural distribution patterns of ^{13}C and ^{2}H with the ratios of these isotopes in their wings (*4*).

We are on the verge of an explosion in the use of stable isotopes to examine a myriad of unanswered ecological questions about animal migrations over a range of geographical scales. Future research will require improved geographical resolution of isotope distribution patterns combined with other chemical and biochemical markers to accurately evaluate the origins of migrating animals. Geologic and hydrologic patterns for Sr, Pb, and S isotopes, which enter animal tissues through the food web, should improve geographical and spatial resolution still further. Researchers are attempting to combine genetic markers with stable isotope markers to better resolve population



Flights of fancy. Patterns of ^{2}H abundance in rainfall (red contours) across the United States and Canada during months when the average temperature exceeds 0°C (the growing season). Red dots represent rainfall sampling stations. The abundance of ^{2}H in rainfall was greatest in the southeastern United States and least in northwestern Canada. Average ^{2}H values are ratios of this isotope to normal hydrogen (relative to the Vienna standard mean ocean water reference). Precipitation and isotope data are from the International Atomic Energy Agency and Environment Canada for the 30-year period 1969–1999.

structures and to establish linkages between migrating populations (*7*). Finally, isotope-ratio mass spectrometry is sufficiently advanced that automated accessible analyses are available at relatively low cost. There is, however, an urgent need to standardize stable isotope data among laboratories. Despite these technological growing pains, we can soon expect intriguing breakthroughs in our understanding of the global migrations of animal species ranging from migratory bats and songbirds to butterflies.

References

1. D. R. Rubenstein *et al.*, *Science* **295**, 1062 (2002).
2. A. B. Cormie, H. P. Schwarcz, J. Gray, *Geochim. Cosmochim. Acta* **58**, 365 (1994).
3. K. A. Hobson, L. I. Wassenaar, *Oecologia* **109**, 142 (1997).
4. L. I. Wassenaar, K. A. Hobson, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 15436 (1998).
5. T. D. Meehan *et al.*, *Condor* **103**, 11 (2001).
6. J. F. Kelly, V. Atudorei, Z. D. Sharp, D. M. Finch, *Oecologia* **130**, 216 (2002).
7. M. S. Webster *et al.*, *Trends Ecol. Evol.* **17**, 76 (2002).

PERSPECTIVES: BIOMEDICINE

Under Pressure

James S. Friedman and Michael A. Walter

Sight is possibly the most valued of the five senses. The loss of vision through disease affects countless millions worldwide and will become an increasing problem as the global population ages. One common cause of sight loss is glaucoma, a disease characterized by the gradual loss of peripheral vision (see the figure). It is predicted that at least 66 million people worldwide have glaucoma, and that this disease leads to bilateral blindness in more than 6 million individuals (*1*). Glaucoma is the principal cause of blindness among African Americans and the second leading cause of blindness among Caucasians. On page 1077 of this issue, Sarfarazi, Rezaie, and their colleagues (*2*) show that mutations in the *OPTN* gene, which encodes the optineurin protein, are responsible for a significant proportion of cases of primary open-angle glaucoma, the most common form of this disease.

The Sarfarazi laboratory has an impressive track record in the field of glaucoma genetics. This group was the first to map and isolate *CYP1B1*, the gene mutated in about 85% of congenital glaucoma patients (*3, 4*). In their new study, Rezaie *et al.* (*2*) applied genetic linkage analysis to members of a single family (pedigree) in whom glaucoma segregated as an autosomal dominant trait with the GLC1E locus on chromosome 10p14–p15 (*5*). After reducing the GLC1E critical region to a length of 5 cM and excluding four other genes, the authors selected *OPTN* as their candidate gene. They found that in members of this large glaucoma pedigree the *OPTN* gene contained a missense mutation that resulted in a $Glu^{50} \rightarrow$ Lys (E50K) amino acid change in the optineurin protein. A broader search of 54 additional adult-onset glaucoma families with normal to moderately elevated eye pressure (which can be a predictor of glaucoma) uncovered several additional *OPTN* mutations. Some of these families carried the E50K mutation, one family carried an insertion in *OPTN* resulting in a premature stop codon, and one family had an $Arg^{545} \rightarrow$ Gln residue change. A "risk-associated" $Met^{98} \rightarrow$ Lys change was present in 12.1% of individuals without a family history of glaucoma and in 17.8% of their kindreds with glaucoma. The high frequency of the E50K mutation in glaucoma patients was statistically significant, even though the risk-associated amino acid change is present in the normal population at a frequency of about 2%.

Rezaie *et al.* (*2*) detected expression of *OPTN* mRNA and protein in the tissues of healthy individuals. With Northern blot analysis, they found *OPTN* mRNA expression in the trabecular meshwork and nonpigmented ciliary epithelium of the human eye. In addition, human optineurin is expressed in retina epithelial cells, fibroblasts, skeletal muscle, and kidney. Immunoblotting experiments revealed that optineurin is present in the aqueous humor (the liquid in the anterior chamber of the eye) of a variety of species. Immunocytochemistry confirmed that optineurin is a secreted protein localized in the Golgi apparatus of cells. Cultured dermal fibroblasts derived from a patient with an E50K missense mutation in *OPTN* produced less optineurin than fibroblasts from a healthy control. This suggests that loss of one allele of the *OPTN* gene through mutation (haploinsufficiency) could be the underlying cause of glaucoma. The biochemical and molecular analysis by Rezaie *et al.*, coupled with their genetic data, clearly shows that mutations in *OPTN* are responsible for many cases of adult-onset primary open-angle glaucoma.

Tunnel vision. "Self-Portrait with Bandaged Ear" by Vincent van Gogh as seen by an individual with normal vision (**top**) and by a patient with peripheral vision loss associated with the early stages of glaucoma (**bottom**).

CREDIT: GIRAUDON/ART RESOURCE, NY

Six loci potentially harboring genes involved in this form of glaucoma have been mapped, but, so far, only one other candidate gene, *TIGR/MYOC*, has been identified (*6*). Mutations in *TIGR/MYOC* are present in about 4% of familial primary open-angle glaucoma cases. Among primary open-angle glaucoma patients, 16.7% of low- to moderate-tension glaucoma families carry *OPTN* mutations (*6*). This finding confirms that mutations in the *OPTN* gene are involved in a significant proportion of primary open-angle glaucoma cases. Examining patients with high- and low-pressure forms of this disease will allow the frequency of *OPTN* mutations to be determined.

The Rezaie *et al.* study delivers the gift of a new protein to researchers working to understand glaucoma pathogenesis and to find therapeutic interventions for treating this blinding disease. Optineurin is known to interact with several important proteins including huntingtin, the protein mutated in a neurodegenerative disease called Huntington's (*7*). In addition, optineurin may be a component of the tumor necrosis factor–α signaling pathway, which regulates programmed cell death (*8*). Rezaie and coworkers speculate that optineurin's normal protective task in this pathway may be disrupted in glaucoma patients carrying *OPTN* mutations. Interestingly, *TIGR/MYOC* may also be part of a neuroprotective response (*9*). The identification of more genes implicated in glaucoma increases the possibility that we may elucidate a common pathway that is disrupted in different forms of this disease. Recently, work by Vincent *et al.* uncovered a potential modifying effect of the *CYP1B1* gene on *TIGR/MYOC* (*10*). Individuals with

The authors are in the Departments of Ophthalmology and Medical Genetics, University of Alberta, Edmonton, T6G 2S2 Alberta, Canada. E-mail: mwalter@ualberta.ca