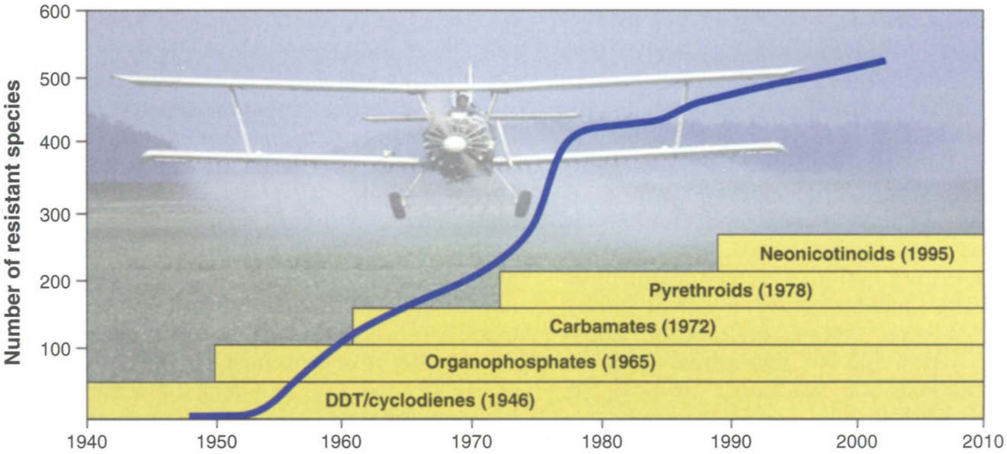
PERSPECTIVES: EVOLUTIONARY GENETICS

Insecticide Resistance on the Move

I. Denholm, G. J. Devine, M. S. Williamson

Like drug resistance in microbes, the evolution of insecticide resistance by insects threatens human welfare through its impact on crop protection and disease transmission. The introduction of new insecticides has resulted in a rapid increase in resistance (see the figure), with many species now resisting several classes of insecticide. Predicting and managing resistance requires information on cross-resistance characteristics and on the origins, selection, and spread of resistance genes. On page 2253 of this issue, Daborn *et al.* address these aspects and extend the number of mechanisms for which detailed information about their molecular and population genetics is now available (*1*).

Daborn *et al.* have investigated the genetics of a mechanism of DDT resistance (DDT-R) long known to exist in *Drosophila melanogaster*. Initial work implicated enhanced detoxification of DDT by cytochrome P450–dependent monooxygenase enzymes as the primary cause of DDT-R, but it was not known which of the many P450 genes in *Drosophila* were up-regulated or altered in resistant individuals. This breakthrough was achieved a year ago (*2*). The availability of the full genome sequence for *Drosophila* made it possible to screen a microarray chip containing all of the 90 known P450 coding regions for differential expression in resistant and susceptible strains. Resistance was associated with just one P450 gene, *Cyp6g1*, which is now shown (*1*) to also be overexpressed in 28 strains of DDT-resistant *D. melanogaster* collected throughout the world over the last four decades. Moreover, the resistant *Cyp6g1* alleles in these strains have remarkable homology, as shown by intron sequencing and the presence of a conserved transposable element insertion at the 5′ end of the gene. This implies that the resistance allele had a single origin and subsequently spread around the world.



Increasing insecticide resistance threatens pest and disease management. Developed in 1939, DDT was the first insecticide to be used on a global scale. The first case of DDT resistance was recorded in 1946, and this signaled the beginning of a continuing war of attrition. Over the next 60 years, the number of resistant arthropod species (blue line) increased rapidly in response to the development and use of insecticides. (Yellow bars denote time over which particular insecticide groups have been used, and dates in parentheses are the year in which resistance was first documented.)

PHOTO SOURCE: DOUG WILSON/USDA

These findings have important implications for understanding how resistance evolves and the threats it poses to sustainable pest and disease management. The results reinforce the hypothesis that resistance genes need not arise de novo to cause problems in a particular region. Through natural migration or human-mediated transport, resistant pests have the capacity to disperse and transfer genes over large areas in very short periods of time. This phenomenon has previously been described for mosquitoes that resist insecticides by amplification of insecticide-detoxifying carboxylesterase genes. Sequencing of DNA surrounding these genes implied a common origin and spread, probably through passive migration on ships or airplanes (*3*). Similar geographic spread has been confirmed for crop pests such as aphids and whiteflies, no doubt facilitated by the extensive global trade in plant produce [e.g., (*4*)]. The ease with which resistance genes can be transferred over large areas, both nationally and internationally, emphasizes that strategies for resistance management need to be implemented on an area-wide, even global, basis. A recent outbreak of malaria in South Africa was correlated with the spread of resistant mosquitoes from neighboring Mozambique (*5*).

Cyp6g1 is reported to have an unusually broad substrate specificity. It appears to resist not only DDT but also a range of other insecticide groups, including organophosphates, neonicotinoids (recently developed analogs of nicotine), and benzoylphenylureas (compounds interfering with insect development). These groups encompass strikingly different modes of action and might be considered ideal candidates for rotation strategies aimed at avoiding continuous selection for the same resistance mechanism. Patterns of cross-resistance are, however, very difficult to predict, particularly for detoxification mechanisms, where specificity may depend on subtle features of the chemical structure of insecticides. One important practical consequence is that as such broad-spectrum mechanisms accumulate in pest populations, the risk of resistance extending to new agents increases. The broad specificity of *Cyp6g1* needs to be examined further, for example, by testing insects genetically modified to express the resistance allele in an otherwise fully susceptible background (*1*). If broad cross-resistance is confirmed, these modified insects provide an excellent model for detailed empirical research and modeling of interactions between the enzyme and a range of xenobiotic molecules.

Drosophila has a long history as the model insect in classical genetics and molecular biology, culminating in the recent publication of the full *Drosophila* genome sequence (*6*). *Drosophila* is not a major crop pest or a primary target for commercial applications of insecticides. However, the wealth of tools for the lo-

---

The authors are with Rothamsted Research, Harpenden, Hertfordshire AL5 2JQ, UK. E-mail: ian.denholm@bbsrc.ac.uk

calization, cloning, and identification of genes make it invaluable for studying insecticide resistance phenotypes. For example, *Drosophila* genetic studies led to the first identification of a point mutation in a protein (the γ-aminobutyric acid–gated chloride channel in nerve membranes) that confers target site insensitivity to cyclodienes (*7*). *Drosophila* genetics also played a key role in the characterization of two other major target site mechanisms identified in insects: acetylcholinesterase insensitivity to organophosphates and carbamates (*8*) and knockdown resistance to pyrethroids (*9*). Daborn *et al.* (*1*) provide another elegant example of how this species can be exploited to benefit both basic and applied research on insecticide resistance. To take full advantage of the *Drosophila* model, it needs to be tested through access to genomics data for species of more direct practical concern. The amount of genome sequence available is changing rapidly. The whole genome sequence of *Anopheles gambiae*—the primary vector of malaria—has recently been completed (*10*), and rumors abound of sequencing projects involving crop pests and other disease vectors, either in progress or close to completion. Provided completion of these projects yields publicly accessible data, the opportunities for investigating the homology, origins, and organization of resistance traits at the molecular level, and for comparing these traits across a broad range of taxa, will be very exciting indeed.

References and Notes

1. P. Daborn *et al.*, *Science* **297**, 2253 (2002).
2. P. Daborn *et al.*, *MGG Mol. Genet. Genomics* **266**, 556 (2001).
3. M. Raymond, A. Callaghan, P. Fort, N. Pasteur, *Nature* **350**, 151 (1991).
4. L. Field, A. L. Devonshire, *Biochem. J.* **330**, 169 (1998).
5. B. J. Sina, K. Aultman, *Trends Parasitol.* **17**, 305 (2001).
6. M. D. Adams *et al.*, *Science* **287**, 2185 (2000).
7. R. H. ffrench-Constant, T. A. Rocheleau, J. C. Steichen, A. E. Chalmers, *Nature* **363**, 449 (1993).
8. A. Mutero, M. Pralavorio, J. M. Bride, D. Fournier, *Proc. Natl. Acad. Sci. U.S.A.* **91**, 5922 (1994).
9. M. S. Williamson, D. Martinez-Torres, C. A. Hick, A. L. Devonshire, *Mol. Gen. Genet.* **252**, 51 (1996).
10. The complete *Anopheles gambiae* genome sequence is freely available at ftp://ftp.ncbi.nih.gov/genbank/genomes/Anopheles_gambiae. An initial annotation of the sequence can be found at www.ensembl.org/Anopheles_gambiae.

PERSPECTIVES: CLIMATE

The Ocean's Role in Atlantic Climate Variability

Martin Visbeck

Large climatic variations during the ice ages have been linked to changes in the circulation of the Atlantic Ocean (*1*). During the last 10,000 years, we have enjoyed a more stable climate with comparatively mild century-scale fluctuations (*2*). Today, a substantial part of the global year-to-year climatic variability is caused by the El Niño–Southern Oscillation in the Pacific Ocean (*3*).

The Pacific is three times as wide along the equator as the Atlantic and can effortlessly influence climate around the globe. The influence of the Atlantic is less wide-ranging but can nevertheless be substantial, especially if its circulation changes. One part of the international research program CLIVAR (Climate Variability and Predictability) is beginning to shed light on the mechanisms and predictability of Atlantic climate variability (*4*).

Air-sea interactions in the tropical Atlantic cause substantial year-to-year variability in the amount and timing of rainfall along the east coast of South America from Brazil to the Caribbean in boreal spring (March to May) and in western sub-Saharan Africa in boreal fall (August to September). These regions are near the Intertropical Convergence Zone (ITCZ), where very warm surface temperatures cause rapid, high-reaching cloud formation associated with strong precipitation (see the figure). Changes in the location of the warmest surface temperature cause north-south displacements of the ITCZ and substantial regional rainfall variability (*5*).

In the equatorial Atlantic, changes in the north-to-south temperature distribution cause most of the observed ITCZ variability. This is quite different from the Pacific, where El Niño is associated with changes in the west-to-east surface temperature. Atlantic surface-temperature anomalies just north of the Equator can be triggered by El Niño, as well as by changes in the strength of the trade winds associated with the North Atlantic Oscillation (NAO) (see below). Changes in large-scale ocean circulation may also alter tropical temperature gradients and thus modulate the location and strength of the Atlantic ITCZ. With rapid progress in the understanding of tropical Atlantic variability (TAV), prospects are good for improved seasonal-to-interannual rainfall predictions in the tropical Atlantic.

Atmospheric variability in the extratropical Northern Hemisphere winter (December through March) is dominated by the NAO (*6*, *7*). When the NAO is in its positive phase, low-pressure anomalies over Iceland and the Arctic combine with high-pressure anomalies across the subtropical Atlantic to produce stronger-than-average westerly winds across the mid-latitudes (see the figure). During this phase, climate is colder and drier than average over the northwest Atlantic and the Mediterranean, whereas conditions are warmer and wetter than average in northern Europe and the eastern United States.

Extensive climate impacts have been documented for the NAO (*4*), and scientists speculate about its interaction with global warming (*8*). The phase of the NAO appears to be largely driven by atmospheric weather noise, with changes in ocean sea-surface temperatures having only a moderate effect on the NAO (*9*). However, the NAO causes extensive changes in the surface wind field, which in turn strongly affect upper-ocean temperatures and circulation (*10*).

Surface temperatures and wind-driven currents change within days, whereas the basin-scale ocean circulation takes up to a decade to fully adjust to changes in atmospheric conditions (*11*). This constant game of oceanic catch-up leads to marked decadal variability in ocean properties forced by month-to-month atmospheric variability (*12*).

Seasonal or longer term prediction of the NAO would have enormous socioeconomic impacts: Who would not like to know a few months in advance when ski conditions in the Alps will be best, or what the price for hydroelectric energy in Norway and Turkey might be? But recent studies are not optimistic about the accuracy of seasonal-to-interannual NAO forecasts (*4*, *9*).

The Atlantic Ocean helps to mediate the imbalance in net radiation between the tropics (where more heat is received by the Sun) and the polar regions (where more heat is radiated into space). It does so through ocean currents that transport warm water from the tropical Atlantic to the subpolar Arctic region (see the figure).

The author is in the Department of Earth and Environmental Sciences, Lamont-Doherty Earth Observatory, Columbia University, Palisades, NY 10960, USA. E-mail: visbeck@ldeo.columbia.edu