

within species: lethal and sterile mutations are nearly completely recessive in heterozygotes, while less deleterious alleles are more nearly additive¹⁰. (Kacser and Burns¹¹ have explained this well-known observation as the result of loss-of-function mutations affecting enzymes in

report¹³. One would also expect that, because the large 'X-chromosome effect' in crosses is due entirely to recessivity and not to differential rates of evolutionary change, one would see no disproportionate concentration of 'sterility genes' on the X chromosome. There is some evidence

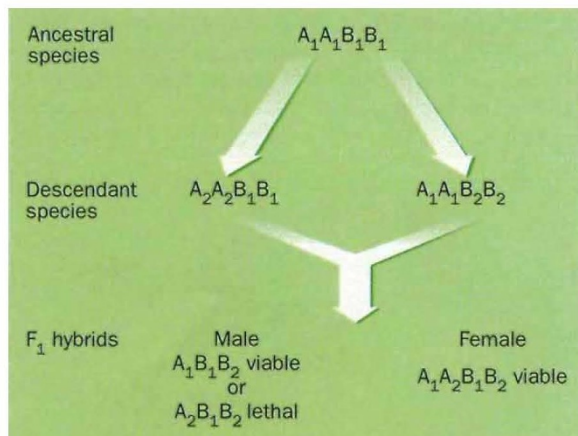


FIG. 2. One possible model for Haldane's rule. In the species involved here, males are heterogametic, having locus A on the X chromosome and locus B on an autosome. An ancestral species fixed for alleles A_1 and B_1 speciates, with one descendant becoming fixed for allele A_2 and the other for allele B_2 . Allele A_2 is inactive on a hybrid (B_1B_2) genetic background. This loss of function at locus A causes hybrid inviability. As shown, male hybrids from one reciprocal cross are lethal because they carry only the inactive A_2 allele. Female hybrids from both crosses have one inactive A_2 allele and one active A_1 allele; according to the model of Kacser and Burns¹¹, these females are viable because the loss-of-function allele A_2 acts as a recessive. Haldane's rule is therefore obeyed in one reciprocal cross. There are many other possible models, which may involve complicated interactions between several hybrid lethal and suppressor genes.

multistep pathways.) Although alleles causing hybrid sterility and inviability must behave normally within species, they could fail to function on a hybrid genetic background. As Dobzhansky and Muller noted half a century ago^{4,12}, these deleterious epistatic interactions involve at least two loci, a 'hybrid lethal' and a 'suppressor'. Figure 2 gives one example of how such interactions might produce Haldane's rule. When combined with the additional proviso (also obeyed within species), that alleles causing sterility usually affect only one sex whereas those causing inviability usually affect both sexes, the new recessivity model explains Haldane's rule in all taxa and the large effect of X chromosomes in heterogametic hybrids.

Orr's theory may, of course, prove incorrect, but it yields several predictions that can be tested. In species obeying Haldane's rule, for example, one would expect on occasion to see reproductive isolation in the homogametic sex in F₂ hybrids, which could then become homozygous for recessive sterility or inviability genes. This phenomenon has been observed, as described in a new

from *Drosophila* that this is true as well (H. Hollocher and C.-I. Wu, personal communication). The proposed recessivity of genes causing postzygotic isolation can be tested by genetically engineering a heterogametic individual that is heterozygous for an X-linked sterility allele and a normal conspecific allele that has been translocated to an autosome. Such a genotype, which could be constructed in *Drosophila*, should recover fertility or viability. Finally, we know almost nothing about the biochemical basis of hybrid sterility or inviability, and Orr's theory must ultimately be tested by working out the genetic and developmental bases of these phenomena.

The most satisfying aspect of the hypothesis is its simplicity: it explains a variety of phenomena with only a few reasonable assumptions, so that one need not invoke different causes of Haldane's rule in

different taxa. Also, by using well-established genetic phenomena within species to explain a pattern discernible only among species, it bridges a gap between micro- and macroevolution. That should appeal to those who believe that speciation can be explained by well-understood principles of evolutionary genetics. □

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Internal smoke

In much of the Western world, smoking has become a deadly sin. The current social orgy of political correctness and righteous indignation (which Daedalus attributes to widespread sexual and economic frustration) has found smokers to be ideal victims. They cause a highly visible and smellable nuisance, offering splendid scope for moral outrage. Furthermore, they are addicted, and can't just dodge the outrage by giving up. Daedalus now comes to their rescue.

His plan exploits the rechargeable blank drug depot he devised last week. It is injected into the patient, who can then take the matching drug at any time and in any dosage. The depot rapidly absorbs it from his bloodstream, and thereafter leaks it slowly back at the ideal level. It can be recharged by a new dose at any time.

This cunning product was invented for cocaine addicts, to damp their wild highs and stave off their withdrawal lows. It could also deliver long-term drugs such as contraceptives, antihypertensives and antipsychotics. But Daedalus is now targeting it at nicotine, the addictive principle of tobacco. Smoking, he points out, has its own chemical logic. Nicotine by itself is rather unstable: it readily reacts with oxygen. It exists in tobacco as stable salts of citric and malic acids. The heat of smoking breaks these up and releases it as vapour. In the body it soon decomposes, either in the liver or by oxidation. So the smoker has to feed his habit many times a day.

DREADCO's chemists are now devising a fatty depot polymer with acidic groups that react rapidly but reversibly with nicotine. The dissociation constant of this reaction equilibrium will be chosen to leak a low, enduring, stable level of nicotine into the bloodstream: just enough to hold off tobacco hunger.

By itself, the new depot injection will not solve the smoker's problems. It would merely allow him to smoke one enormous cigarette every day, or even every week, and be conspicuously virtuous at all other times. To complete the scheme, Daedalus is devising matching nicotine tablets. Their nicotine is stabilized by acid combination, and when ingested is rapidly transferred to the internal depot by a smooth exchange reaction. By topping up his internal depot with an occasional tablet, the ex-smoker will at last be free of tobacco hunger. He will continue to gain the benefits of smoking, whatever they are, without risk to health or popularity. The tobacco companies will survive as the ultimate source of the nicotine. And the indignation industry will have to look for new victims.

David Jones