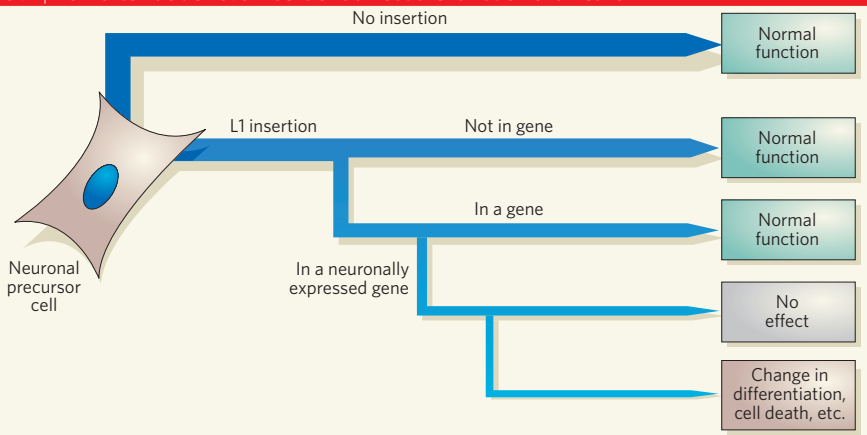
Box 1 | How often do *de novo* insertions affect the function of a neuron?



It is impossible to determine directly the frequency of insertions that occur *in vivo* in human neuronal precursor cells (NPCs), and Muotri *et al.*[2] were not able to quantify this number in transgenic mice. It seems, from stained brain sections, that insertions do not occur more often than once in 10 cells, perhaps only occurring as rarely as once in 1,000 cells. Although a small fraction of cells may appear to have new insertions, it is difficult to extrapolate the activity of an unknown number of highly active L1 elements in a transgenic mouse to the activity of a number of endogenous L1 elements. Most insertions will not occur in genes. If L1 insertion is entirely random, the percentage of insertions into genes would be about 30% — the percentage of the genome that is made up of genes (introns plus exons). Muotri *et al.*[2] have reason to believe that the percentage of gene insertions may be higher than 30% because of non-random insertion. However, to affect neural function, an insertion must occur in a neuronally expressed gene, and the insertion must have an effect on cell fate even when only one of the two copies of a gene is disrupted. Insertions into a single copy of some neuronally expressed genes may have no effect. **E.M.O. & H.H.K.**

However, if the mechanism to create diversity is encoded in the germ line (for example, by the number and activity level of mobile elements), and if diversity is favoured by natural selection, then this mechanism can be maintained through evolution.

Time and further research will determine whether McClintock's hypothesis that mobile elements have a significant role in an organism's development can be extended from maize to humans, and specifically to the function of human neurons. ■

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MALARIA

Fungal allies enlisted

Yannis Michalakis and François Renaud

The mosquito-killing capabilities of fungi can in principle be deployed in the fight against malaria. But long experience of unfulfilled hopes in this complex arena shows the need to proceed cautiously.

Many malaria control measures have centred on the mosquito vector of the *Plasmodium* parasite that causes the disease. Female mosquitoes transmit *Plasmodium* from human to human after feeding on the blood of an infected person — hence the age-old use of bednets, and the more recent attempts to genetically manipulate mosquitoes to make them resistant to parasite infection, or to reduce mosquito populations with insecticides. Two papers in *Science*, by Blanford *et al.*[1] and Scholte *et al.*[2], describe another approach — the deployment of mosquito-killing fungi.

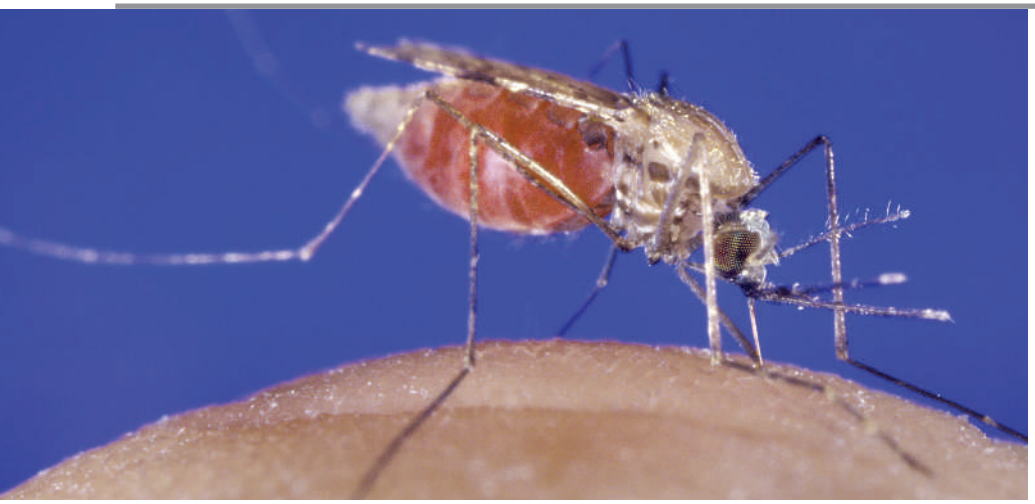
Using mouse malaria as a model system, Blanford and colleagues[1] studied the effects of various isolates of these fungi on mosquitoes. Many isolates induced mosquito mortality of more than 80% within 14 days of infection, a period that corresponds to that in which *Plasmodium* produce offspring in the mosquito that are transmissible to humans. Further experiments with one of the fungal isolates, chosen because it is part of an existing agricultural pesticide, showed that the fungi also have a direct effect on the development of *Plasmodium* in mosquitoes: only 8% of mosquitoes infected with both the parasite and fungi contained transmissible parasite offspring 14 days after exposure to the fungi, compared with 35% infected with *Plasmodium* alone. Putting the effects on mosquitoes and *Plasmodium* development together, fungi could reduce malaria transmission by approximately 80-fold. The effect might be even greater, given that fungal infection also decreases the propensity of infected females to feed on blood.

Blanford *et al.* carried out their experiments with several isolates of two different species of fungi and several malaria clones. They also tested various fungus-containing formulations, applied on nets or solid surfaces for different exposure times, and showed that their conclusions still held. Nonetheless, mouse malaria may have different characteristics from human malaria, and many different factors can come into play when applying research findings in the field.

Some of these issues were addressed by Scholte *et al.*[2], whose research involved trials with cotton sheets impregnated with fungal spores in several dwellings in rural Tanzania. When such sheets are draped or hung in a house, mosquitoes will tend to rest on them — hence their designation as 'resting' sheets. The results confirm Blanford and colleagues' conclusions[1] that mosquito survival is significantly decreased by fungal infection. When Scholte *et al.* fed their data into an epidemiological model to calculate the effect on malaria transmission, the estimated number of infective mosquito bites per person per year dropped from 262 to 64. Increasing the coverage of mosquito resting sites could bring this number down to 10.

So far, so good. But what about the ecological and evolutionary issues that arise? The first is fungal specificity — or lack of it. Two of the isolates used by Blanford *et al.* came from beetles and moths, moth isolates also being used by Scholte and colleagues. The fungi are likely to kill pretty much any insect, and maybe other organisms, that come into contact with them. Although people would probably be better off without most insect species that get into houses, that may not be true for all of them. Lack of specificity might not be a problem, but it merits further research.

Second, there is the question of the possible development of resistance to the fungi. Use of



J. GATHANY/CDC

Figure 1 | Blood sucker. An *Anopheles* mosquito, of a species that transmits malaria, takes a meal.

insecticides against mosquitoes, or drugs such as chloroquine against *Plasmodium*, have both resulted in the advent of resistance to these chemical assaults. What might happen if fungi are deployed as control agents? Could they actually make matters worse?

Mosquitoes might evolve ways to prevent the fungus from entering their body, or limiting its growth if they do become infected. Such forms of resistance are possible, but it seems unlikely that they would intensify *Plasmodium* transmission or virulence. Another form of mosquito resistance might be behavioural. Malaria-transmitting mosquitoes feed on the blood of both humans (Fig. 1) and domestic animals, host preference being genetically determined, at least partially[3,4]. The widespread indoor application of fungi could impose strong selection on mosquito host-preference or resting behaviour, because only mosquitoes feeding or resting indoors would be infected. A shift in host preference towards domestic animals would have a lasting benefit in terms of malaria transmission to humans (human malaria develops only in humans). It could result in increased transmission of disease among domestic animals, but it is perhaps preferable to deal with a problem of economics rather than one of public health.

Another — perhaps more worrying — prospect is that the rate of *Plasmodium* development would accelerate, enabling the parasite to produce its transmissible offspring before the mosquito host is killed by the fungi. This would be a serious outcome, for two reasons. First, it implies that the malaria 'generation time' would decrease, resulting in more malaria per unit of time. We don't really understand why malaria takes so long to become transmissible[5], but the effect of the fungi could be to shift the balance towards faster development. Second, faster development could be associated with higher virulence in humans. The correlation of parasite traits in their different hosts is poorly understood[6], and analyses of the variation of developmental time among *Plasmodium* isolates and its relation to virulence in mosquitoes and vertebrate hosts are called for. A reassuring result in that respect is that, in the mouse model of malaria, *Plasmodium* virulence in the vertebrate and the mosquito are not correlated[7].

Having raised various concerns, we should return to the promise of mosquito-killing fungi for malaria control. The fungi evidently have a strong effect on malaria transmission, and they target the transmitting stage of the mosquito, the blood-feeding adult. The approach is environmentally friendly, at least compared, for example, with spraying larval insecticides on water surfaces. And it can be enhanced by relatively straightforward measures such as increasing the dosages of the fungal spores or the size of the resting sheets, and using both impregnated bednets and resting sheets. There is also the possibility of increasing the longevity of the spores, through fungal-breeding programmes. All in all, we have the prospect of opening a new front in the war on malaria. It is surely an approach worth pursuing. ■

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ENGINEERING

Skimming the surface

Jacob N. Israelachvili

Models of the microscopic contact area between two surfaces work surprisingly well, or fail completely, depending on the aspects of adhesion or friction being investigated. A simulation now shows how the details matter.

What happens at the atomic and molecular level when surfaces come into contact with each other? And how do these events relate to macroscopic properties and observations? These questions, which centre on the phenomena of adhesion and friction, pose challenges not only in engineering but in many other areas of the physical and biological sciences. Finding correlations and models that connect the atomic and macroscopic worlds is not easy. On page 929 of this issue, Luan and Robbins[1] describe the use of molecular dynamics to test the limits of macroscopic descriptions. The novel conclusions that they reach highlight just how important the atomic-scale details can be in controlling the behaviour of surfaces as they adhere to and slide past each other.

Macroscopic theories usually sidestep the atomic structure of matter, and instead view the interacting objects as smooth, with structureless surfaces. Such 'continuum' models of adhesion, a field known as contact or adhesion mechanics, are based on the pioneering theories of Hertz[2,3] and of Johnson, Kendall and Roberts (JKR)[4]. They use linear elasticity theory to describe the deformations of two smooth, curved surfaces when they are pressed together or separated through contact that is non-adhesive (Hertz theory) or adhesive (JKR theory). Adhesive contact means that the surfaces naturally stick to each other. In other words, the surface energy, generally denoted γ, is finite. In air, all surfaces have a finite γ, so they stick to each other provided the surfaces are atomically smooth over their entire macroscopic contact area. In liquids, surfaces — even smooth ones — can repel each other, leading to lubrication rather than friction forces.

JKR theory predicts a remarkably simple equation for the adhesion force F needed to detach a surface of radius R from a flat surface: $F = 3\pi R\gamma$ (Fig. 1, overleaf). Detachment occurs when the surfaces require a negative load in order to separate. The equation can be generalized to other geometries by replacing R with some characteristic length for that geometry. The JKR equation holds surprisingly well, but only for perfectly elastic bodies with atomically smooth surfaces and radii much larger than