POLICY FORUM: INFECTIOUS DISEASE

The Case for Deemphasizing Genomics in Malaria Control

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A frank appraisal of the probable outcome of most molecular/genomics research supposedly aimed at reducing the death toll from malaria shows little likelihood that it could pass the "so what?" test. In this context, it is important to distinguish research that might help to explain retrospectively some biological facts, from research that could actually help to guide disease controllers, especially those working in countries with annual health budgets of less than $10 per person.

I am not arguing that there is no room for improvement in present control techniques to get back to, and then improve upon, the near-eradication of malaria achieved between the 1940s and 1970s in India, Sri Lanka, Venezuela, and Central Asia (*1*), as well as in Zanzibar and other limited areas in tropical Africa (*2*). The kind of research that is needed is mostly fairly simple-minded and goal-oriented fieldwork. Where a molecular method is chosen, this choice should be dictated by its being the best way to solve an existing problem and not because it seems to the researcher and/or the funding agency to be the most modern approach.

In anopheline biology, identification of members of species complexes and molecular methods for these identifications are emphasized. In several cases, these closely related species differ in blood feeding and resting behavior but, unfortunately, seldom to the extent that such knowledge could really help a vector controller. For example, although *Anopheles arabiensis* is less exclusively inclined to bite humans and to rest indoors than *A. gambiae*, the former species is still a formidable vector that requires control, and it spends enough time indoors to be controllable by house spraying or insecticide-treated nets (*3*). Furthermore, if only the totally zoophilic *A. quadriannulatus* exists in an area, it already ought to be apparent that there is no malaria there.

Much effort is being devoted to biochemical and molecular studies of resistance mechanisms and to mapping of resistance genes. It is hard to see how such mapping could help to solve the practical problem of resistance. It is frequently said that understanding biochemical mechanisms will allow predictions about cross-resistance spectra. However, these spectra are quickly and more reliably determined by simple bioassays with the alternative insecticides. Several biochemical or molecular tests can be done on one mosquito, but in those cases where there is a shortage of mosquitoes for testing, it would almost certainly be cheaper to employ more mosquito collectors than one molecular biologist.

There is much excitement about transgenesis as a way to generate strains of mosquito that cannot transmit malaria. If a single dominant gene with these properties could be engineered, this would be an improvement on *Plasmodium* nonsusceptible strains that have already been selected by old-fashioned breeding techniques (*4*). However, without extremely reliable systems for driving the transgenes into wild vector populations, possession of a nontransmitter strain would be of no practical use. Even if a totally reliable gene-driving system were produced, there might well be strong political objections to the irrevocable release of genetically manipulated insects that bite people.

A more feasible and acceptable way of using transgenesis may be to improve the sterile insect technique, which would only require release of nonbiting males (*5*). This method might be applicable to the malaria problem by using it for eradication of residual populations of urban species of vector mosquito. For example, *A. stephensi* might be a prime candidate in Indian cities, after maximal efforts have been made to suppress the populations by legally enforced environmental management. The sterile males would only be effective if the populations were "urban island" ones, with no genetic continuity with the rural form *A. stephensi mysorensis* (*6*). Molecular biologists should be investigating whether or not there is gene flow between these urban and rural forms.

For both vector control and chemotherapy, it would be nice to think that knowing the gene sequences of *Anopheles* and *Plasmodium* species will lead to discovery of targets against which new insecticides or antimalarial drugs can be produced. However, I suspect that any such discoveries would be patented and only developed at prices unaffordable to governments or villagers in tropical countries. Thus, we will still be left with insecticides that were developed primarily for the much more profitable agricultural market and cheap drugs, such as proguanil and dapsone, which were developed long ago but, when used in combination, have been shown in a recent field trial to be effective against multidrug-resistant *P. falciparum* (*7*).

In testing antimalarial drugs in areas of high malaria transmission, it is important to distinguish recurrence of parasites, due to recrudescence of incompletely cured infections, from reinfection due to new mosquito bites. Molecular matching of the parasite clones in the same individuals before and after treatment is, in principle, one way of doing this. However, where most infections are polyclonal, it is difficult to be sure that a clone found after parasite recurrence was not present at low frequency in the mix of clones in that subject before treatment. A better way of distinguishing recrudescence from reinfection was to take a group of treated children (with their mothers) from the highly malarious Tanzanian lowlands to stay at an altitude where there is no local transmission (*8*). A 6-week stay for all of them at a highland mission station cost less and gave a more convincing answer (as well as being more enjoyable for all concerned) than trying to study the recrudescence question by molecular means.

POINT COUNTERPOINT

In development of vaccines, the value of knowing the sequences of certain genes and/or peptides is undeniable. However, progress has been painfully slow, and the 2-month duration of protection from the best currently available vaccine (*9*) is inferior to what can easily be achieved with insecticide-treated nets or house spraying. When better vaccines eventually emerge, they should probably be used in conjunction with vector control to avoid their effects being "swamped" in areas of intense transmission. Such vaccines might even restore immunity lost as a result of the reduction of transmission by vector control. Whether vaccines and vector control synergize will have to be tested in the field and will not be predictable from molecular properties.

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This policy forum is based on the authors' contribution to a debate at a meeting at Oxford University organized by the Royal Society of Tropical Medicine and Hygiene and sister societies.

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