viants continuously generated from the parent, or does it represent the existence of genetically independent alternative phenotypic forms present as minor contaminants in non-clonal parasite populations?

To study this problem Roberts *et al.*[1] prepared 27 clones of *P. falciparum* blood-stage parasites from a cloned culture-adapted parent and compared them for infected erythrocyte surface antigen phenotype as well as for adherence to CD36 or ICAM-1, rosetting with uninfected erythrocytes and autoagglutination. Ten new surface-antigen phenotypes were described in cloned parasites derived from the parent clone. The authors also found modulation of endothelial receptor phenotypes in the cloned parasites — a phenomenon not discovered before. There were numerous examples of modulation such as rosetting-negative to rosetting-positive, autoagglutination-negative to autoagglutination-positive, and ICAM-1 and CD36 adherence-negative to ICAM-1 and CD36 adherence-positive.

One of the most fascinating observations in this report is that clones with the same surface-antigen phenotype have the same combination of receptor phenotypes. Does this imply that the malaria parasite uses an antigenically variant structure on the infected erythrocyte surface to fulfil a functional role as receptor for endothelial cells and erythrocyte rosettes? I have speculated earlier that the opposite must be true — that is, that the receptor for endothelial cells would be antigenically conserved, in order to fulfil function, whereas the variant surface antigen would function only in immune evasion[7]. With the results of Roberts *et al.*, it is now likely that the variant surface antigen is in fact the receptor for endothelial cells. They have demonstrated an extremely rapid rate of spontaneous generation of receptor and antigenic variants, have evidence for a correlation between antigen and receptor phenotypes, and show that numerous endothelial cell proteins can be used *in vitro* to select infected erythrocytes with a corresponding receptor specificity.

How do the asexual deviant parasites take over and dominate the parasite population in immunized hosts? The initial inoculum of asexual parasites into the blood (derived ultimately from sporozoites inoculated by the mosquito and having passed through intermediate stages in the liver) will include different phenotypes of the surface antigen and the receptor(s) for endothelial cells. Different phenotypes will be present even if only one sporozoite was originally inoculated owing to the generation of 2% deviant organisms per generation. Two selective forces will operate at the level of the surface phenotype of infected erythrocytes. Variant antigen phenotypes that had previously infected the individual will elicit specific IgG antibodies that lead to destruction of those infected erythrocytes. Antigen phenotypes never seen by the host will survive by negative selection. If the variant antigen and the receptor phenotype are closely linked genetically (or perhaps are even the same structure), the remaining parasites will express a diversity of receptor phenotypes that will then be acted on by the positive selective force for adherence to microvascular endothelial cells and/or rosette formation. Only those infected cells with receptors for tissue proteins expressed at sufficient level in the host will survive. The endothelial cell-surface proteins used for adherence are expressed differentially depending on diverse autocrine and endocrine effects including cytokine stimulation. So the proteins available for positive selection for adhesion may even vary during the course of a single infection, as the host–parasite battle elicits different cytokines and other effectors of endothelial cell-surface phenotype. Given the capacity of infected erythrocytes to produce antigenic variants and receptor deviants, and dynamic changes in the negative selective forces (antibodies) and positive selective forces (endothelial cell-surface proteins) during the course of infection, the infected erythrocytes that proliferate in each person probably have quite different surface phenotypes at different times during the disease.

Pronounced sequestration of infected erythrocytes in cerebral microvessels occurs in only some malaria cases and causes the special neurological pathology of human cerebral malaria[8]. Whether this pathology ensues will depend not only on the potential of the parasite inoculum to produce deviant parasites that adhere preferentially in cerebral bloodvessels, but on the particular antibody responses and the particular collection of endothelial cell proteins available in the individual. □

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DAEDALUS

Hot stripping

LATHES and milling machines face a subtle contradiction. The workpiece must be rigid enough not to deflect under the cutting tool, yet the cuttings must be flexible enough to bend out of its way. The solution is to take repeated fine cuts from a relatively massive workpiece. But very soft and very hard materials defeat the machinist. Rubber deforms hopelessly away from the cutter, while ceramics refuse to deform even as fine cuttings; they simply shatter.

This contradiction between the rigid workpiece and the flexible cuttings can sometimes be evaded. Soft rubber can be cleanly drilled or machined by first cooling it in liquid nitrogen. It becomes as rigid and brittle as glass, yet does not shatter under the drill or cutter. The reason is simple. Whereas the bulk of the rubber is unmachinably brittle, its surface is warmed into flexibility by the air and the heat of machining. Supported on the rigid interior, it curls off cleanly and smoothly, without tearing or sagging away from the cutter.

So Daedalus is repeating this trick at a higher temperature. Imagine, he says, a standard centre-lathe with a powerful heater mounted just ahead of the cutting tool, and playing on the fast-spinning workpiece beneath. The heater will 'write' a continuous heated strip onto the moving surface. If sufficiently intense and localized, this hot strip will not cool and spread by conduction in the millisecond or so before it is 'read' by the cutter a few millimetres downstream. The bulk of the workpiece will remain cool and rigid. But the cutter will be continuously presented with a softened, red-hot skin, easily detached and peeled away from the firm interior.

Few heaters are intense and local enough for this duty. For metallic, electrically conducting workpieces, an arc-welding electrode seems feasible. Daedalus likes the idea of recycling the heat of cutting, by guiding the red-hot strip of freshly cut metal back onto the metal about to be cut; but the heat transfer would probably be too poor.

His real goal, however, is to machine hard, brittle materials such as glass and ceramics. Such insulating and non-combustible substances would have to be spot-heated by a powerful focused laser. Then, like liquid-nitrogen-cooled rubber, they would yield to the lathe. Cups, saucers, plates and holloware could be machined to close tolerances; more significantly, so could big telescope mirrors. And a numerically controlled laser-heated milling machine could form anything from rococo cut-glass decanters to ceramic turbine blades of matchless perfection.

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