rather than, as suggested by Fischer *et al.*, the effect of CsA on the kinetics of PPIase modification and inactivation. Second, the kinetic effects of CsA indicate that PPIase must be subject to processes of probable physiological significance such as protein-modification cooperativity, conformational isomerism and/or modification-induced protein unfolding^{3,4}.

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Fertility and cystic fibrosis

SIR—In a recently published case-control study¹, we demonstrated that cystic fibrosis (CF) carriers do not have higher fertility (measured by completed family size) than do matched controls. Unlike most previous studies, our analysis corrected for ascertainment bias. We also examined birth interval as an indicator of fecundity. A CF gene would gradually increase in frequency if carriers have shorter than average birth intervals (and thus shorter generation times), even in the absence of a fertility difference. Although there was a trend toward shorter birth intervals in CF carrier families, we concluded that this probably resulted from ascertainment bias. Pritchard² made the useful suggestion that birth intervals should be compared after matching cases and controls for completed family size. Here I report the results of such an analysis.

As in our previous study, I identified 143 carrier couples as grandparents of individuals affected with cystic fibrosis. The affected individuals were ascertained from clinical records of the Intermountain Cystic Fibrosis Center, Salt Lake City. Control couples were drawn from a computerized genealogical database containing 1.25 million members and matched on the basis of father's and mother's ages, date of marriage, and completed family size. Analysis was restricted to those case and control couples in which both members survived at least to age 50.

Twenty replicate sets of matched control couples (143 couples in each set) were drawn randomly from the database. The average interval between marriage and first birth among carrier couples (634 days) was less than that of controls in only 11 of 20 comparisons. Couples with intervals of less than 40 weeks were excluded from this comparison. The average between-birth interval among carriers (1,103 days) exceeded that of controls in 19 of 20 comparisons. These

results show that, after matching for completed family size, there is no evidence for greater fecundity in CF carriers than in controls.

Interpretation of these findings should be tempered with the caution that the present-day frequency of CF could be generated by a selective advantage of only 2 per cent¹. Such small differences in completed family size and birth intervals are fairly difficult to detect statistically³. Nonetheless, these results, along with the uneven prevalence of CF in different ethnic groups, argue against a reproductive advantage for CF carriers. The high incidence of CF in some European populations seems more likely to be due to genetic drift or disease resistance (see for example ref. 4).

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Erythrocyte knobs and malaria

SIR—The recent report¹ of cytoadherence by erythrocytes infected with knobless *Plasmodium falciparum* needs to be set in the context of a large body of work originating in my laboratory. This work has clearly demonstrated that the numerous small protuberances on the surface of infected erythrocytes, which we called knobs, are important for the biology of falciparum malaria. It has also shown that specific proteins are exported by intracellular parasites and inserted at the membrane of the host cell, as summarized in ref. 2.

In *P. falciparum*, knobs appear on the surface of erythrocytes infected with asexual parasites about half-way through the 48-hour cycle of development. Their appearance is correlated with cytoadherence to endothelial cells and consequent sequestration in capillaries of certain organs, including the brain. This sequestration keeps the later-stage parasites away from the spleen, the chief organ for their destruction. It is also important in pathogenesis of the disease.

All falciparum parasites form knobs and are cytoadherent *in vivo*. Furthermore, cytoadherence is at the knobs, not at other parts of the erythrocyte. Under *in vitro* conditions or in splenectomized hosts, where there is no selective pressure by the spleen, knobs and cytoadherence may be lost independently either phenotypically or genotypically. Four phenotypes are possible with regard to these traits. K^+C^+ (both with knobs and

cytoadherent) is the only one known to occur naturally. K^+C^- and K^-C^- have been obtained from several isolates either *in vitro* or in splenectomized monkeys. The fourth, K^-C^+ , described in ref. 1, was selected *in vitro* from a subline of the Palo Alto/Uganda strain isolated in 1966 (ref. 3) and since maintained in monkeys or in culture. Its cytoadherence has been demonstrated only *in vitro*; cytoadherence *in vivo* remains to be shown. If it is cytoadherent *in vivo* and can give a patent infection in intact *Aotus* monkeys, then such a K^-C^+ strain could exist in nature, unlike both the K^+C^- and K^-C^- strains.

Genotypically K^-C^- clones adapted to *Aotus* erythrocytes *in vitro* produce very light, barely detectable infections in intact *Aotus* monkeys⁴. Such monkeys, however, show resistance to challenge by an *Aotus*-adapted K^+C^+ wild-type strain. This is analogous to viral vaccination with a live attenuated strain. This promising approach could be developed by engineering a K^-C^- clone genetically unable to form gametocytes and hence not able to recombine in nature with a virulent strain.

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Mycoplasma control

SIR—The three antibiotics that Hay *et al.* report¹ using to eliminate mycoplasma from infected cell lines have been superseded by the considerably more effective 4-quinolone group of antibiotics, such as Ciprofloxacin.

In a recent study² of 26 cell lines treated with Ciprofloxacin we found no evidence of cytotoxicity, no treatment failures, and the elimination of the most prevalent *Mycoplasma* species, including *M. arginini*, *M. fermentans*, *M. hyorhinis* and *M. orale*. A 4-quinolone antibiotic is specifically marketed for the elimination of mycoplasmas from infected cell lines by Dainippon Pharmaceutical Co. Ltd.

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