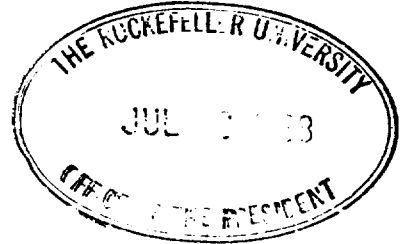# MEMORANDUM

THE ROCKEFELLER UNIVERSITY

TO: Joshua Lederberg
FROM: George A.M. Cross
SUBJECT: Unfinished business (Inoki)
DATE: 7/6/88

Josh -

To briefly respond to your questions:

I am sure that Inoki's experiments demonstrated selection (subsequent to the brief incubation in antiserum). However, as I take every appropriate opportunity to re-iterate in written and oral presentations, the possibility that external perturbations influence rates of antigenic switching has not been ruled out. Although extrinsic factors may not be the primary determinant, they could be very significant under some conditions. In the specific case of activation of (albeit a select subset of) VSG gene transcription in the Tsetse, we are probably seeing some degree of environmental control. However, the process could be entirely stochastic, determined by DNA sequences and VSG gene environment. There are hints that some of the VSG gene flanking sequences could be relevant to recombination, but no definitive evidence.

So far as our own experiments go, they are on hold. We published a set of experiments, widely regarded as the most definitive study in the field, on the rate of phenotypic switching in vitro, in the absence of immune selection. The rates are very low, around 10^{-7} per generation. However, due to lack of persuasion, I have not yet been able to have someone go to the next step, which is to measure the underlying rates of gene rearrangement, which I suspect may be 1-2 orders of magnitude higher, leading either (frequently) to the same phenotype, or else no change in phenotype. A minimum value for the former rate could be derived experimentally with a relatively obvious strategy, but a lot of tedious work. It is more difficult to devise an experimental strategy to measure the latter value.

All of this is presumably related to (wishfully specific) mechanisms for recombination in tryps. On that subject I regret that we have not even the first word, let alone the final!

Thank you for your interest.