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A Tribute to the People of California

DEPARTMENT OF BIOLOGICAL SCIENCES

SANTA BARBARA, CALIFORNIA 93106

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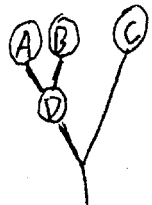
Dr. Theodosius Dobzhansky
The Rockefeller University
New York, New York 10021

Dear Doby:

I enjoyed your letter very much. Yes, I did take your comments at the Boston meeting as being friendly and will admit that Jukes and I have enjoyed being "devil's advocates." The term "non-Darwinian evolution," which everyone hates (except Leigh Van Valen), was at least in part intended to upset people, and it has certainly done that.

The approximation to the Poisson distribution of amino acid related base changes is extremely interesting in that it indicates that the distribution of possible changes is very broad. Nevertheless, the approximation is almost certainly spurious in my estimation. Thus in hemoglobins, the Poisson is approximated without assuming any unchanging sites; in cytochrome c one must assume at least two classes of sites, changeable and non-changeable, hyperchangeable, and invariant. The truth is--and I worked this out several years ago--one gets an even closer fit if one assumes five classes of variability, and the most reasonable assumption is that there is a more-or-less continuous gradation of tendency to vary. I think this will eventually fall apart when there are enough cytochrome c sequences in; Margoliash and Fitch have made a firm prediction that there are 29 sites that are uniform in all eukaryotes, but I will not be surprised to see this prediction fail! Nor will Fitch, at least; he is in theoretical agreement on this point. But it is interesting that the Poisson thing holds up as well as it does so far.

Investigations of the constant rate of evolutionary change in homologous proteins do not require any precision in estimates based on paleontological evidence. The scheme is formally very simple: given three homologous proteins, two will be mutally more closely related than either is to C, and the distances AB, AC, and BC can be measured, then the distance from a common ancestor D to A and to B can be calculated; the formula is $AD = 0.5(AB + AC - BC)$ one asks is AD equal to BD? Because regardless of the paleontological descendant is the same for both lines of descent. The only



difficulty turns out to be that the "distances" AB, AC, and BC in terms of numbers of base substitutions--cannot be known with any degree of certainty. To the extent that they can be estimated--using the assumption that the Poisson distribution is valid, incidentally--AB does seem to be equal to BD in most cases, within the limits of stochastic variation. In fact it is very strikingly so. Again, this very striking and remarkable relationship may be at least in part spurious, but it is very interesting.

As you have pointed out, it is not really necessary to have equal rates of evolution for homologous proteins, even with evolution by random walk. One of the puzzling things about the general observation is that the rates of evolution of lines of descent with very different average generation spans--such as the human-rodent divergence--show the same kind of (apparent) identity of evolutionary rate. If these changes are due mostly to mutation pressure, the only rational conclusion is that the (base-substitution) mutation rate is directly proportional to the generation span when expressed in terms of mutation per generation--since it appears to be constant when expressed in terms of mutations per year. Weird.

Clarke mentions that guinea pig insulin is an obvious exception to the general rule, as Jukes and I also pointed out. But Arnheim, in an interesting paper, suggests that it is not. He found that chicken and duck lysozymes are very similar, while duck and goose lysozymes are very dissimilar. Since ducks are more closely related to geese than to chickens, this suggested that goose lysozyme had evolved at an unusually rapid rate. I noted the similarity with the case of guinea pig insulin, and suggested that in each case there had been a gene duplication in the distant past, long before the chicken-duck divergence in the case of lysozymes, and long before the mammalian order divergences in the case of insulin. Then, perhaps, in each case the product of one of the duplicated genes had become a minor component, the other the major component; in guinea pigs and in geese the major components had become replaced by the minor components. Comparing duck and goose lysozymes, or human and guinea pig insulins, then, was like comparing alpha and beta hemoglobin chains.

Arnheim was able to substantiate this hypothesis in the lysozyme case. He found that there had indeed been such a gene duplication: swans have both chicken-like and goose-like lysozymes! Other workers have noted that mammals do indeed have minor components of insulin that are similar but not identical to the major components. It remains to be seen whether the minor components of other mammals closely resemble the major component of guinea pig insulin.

I would appreciate references to your papers with Wright and Pavlovsky on random drift and founder effect.

In the mut-T case, mutation is not "random" with respect to base changes, but presumably it is random with respect to adaptive changes. I think this is what is usually meant by random mutation. Surely many unfavorable mutations must be eliminated and, yes, there is obviously ample opportunity to select superior lines--as Gibson et al. have shown and as Francisco has shown in analogous experiments.

On the question of a dichotomy of selection vs. non-selection: this is the crux. If random-walk evolution is a minor factor in molecular evolution, as you believe, then there can be a continuous spectrum of adaptive advantages and disadvantages associated with base substitutions, with a small but reasonable proportion falling within the range of $\pm 1/(2N_e)$, the range in which drift is more effective than selection. However, if it is true as Jukes and I have maintained, that a large proportion of molecular changes have been due to drift, then it is necessary to have a very much larger proportion of mutations within this range than occurs above it (i.e., than occurs with selective advantages greater than $1/(2N_e)$. This is simply because selection is so very much more likely to lead to fixation than is drift. So we will have to support and defend the notion that there is a dichotomy. Still, this is just to say that there are many potential changes that hardly matter at all, and that of those changes that <u>do</u> matter, nearly all are for the worse.

I am going to go ahead, at least for the present, with my commitment to serve as an editor of the Springer-Verlag Journal of Molecular Evolution. Tom is quitting in disgust over the Oparin matter and over what he justifiably feels is arbitrary high-handedness in the management of this journal. I must say I prefer the American system of non-profit journals run by volunteer editorial boards.

Are you and Francisco coming to Davis?

Francisco has accepted my invitation to come give some lectures here. I will be writing very soom to him in order to arrange dates and such. We are all looking forward to hearing from an unusually creative and original man.

Yours sincerely,

Jack

Jack King

Personal note: I hope that, in the end, we will have been more than just challenging and disruptive. My ultimate goal would be to bring together Dobzhansky and Ayala with Kimura and Crow! JK.