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SANTA BARBARA • SANTA CRUZ

DEPARTMENT OF BIOLOGICAL SCIENCES

SANTA BARBARA, CALIFORNIA 93106

May 21, 1970

Dr. Th. Dobzhansky
The Rockefeller University
New York, New York

Dear Dr. Dobzhansky:

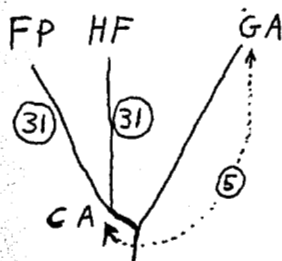
There are some letters I have needed to write to Drs. Ayala and Dobzhansky, mostly about some preprints I wanted to send around. To save energy and xerography expense, I am writing to you jointly, I hope you don't mind. Most interesting is the paper by Gibson, Scheppe and Cox, which you may have seen. It was widely circulated for comment. I suggested that the authors should discuss Francisco's mutation-adaptation work, which has such a strong parallel with the E. coli mutator experiment. Both seem to substantiate the fact that for an evolving organism there is an optimal level of mutation that may be higher than the level that could be attained if selection were uniformly directed at lowering the mutation rate. Also they should probably refer to Dr. Richmond's suggestion that such a competition experiment be done --- though I think that the results are somewhat different than Dr. Richmond expected. To tell the truth they are different than what I would have expected too.

At the Boston meeting you rose to suggest that I really didn't really believe what I had been saying, and genuinely intended it as a complement; I genuinely felt complemented. But actually I do believe what I said, or more accurately, I said what I believed. If one continues to say what he believes, and also continues to question and examine his beliefs, he will eventually and inevitably contradict himself.

Specifically, the hypothesis of the prevalence of non-Darwinian evolutionary change at the molecular level has rested primarily on four legs: (1) The amount of selection required to account for the panselectionist hypothesis results in far too great a genetic load ("cost of evolution"). This argument has been used by Kimura, but was rejected by King & Jukes, having been demolished in advance by Sved and Maynard Smith using a certain model involving continuously distributed factors affecting fitness. (2) The apparent randomness of amino acid composition: amino acid composition can be predicted, within limits, by random permutations of DNA bases read by the genetic code. We discussed and rejected as improbable McKay's suggestion that the code evolved to fit the amino acid composition, rather than the other way around. Ernst Mayr felt that there was something wrong

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with the argument, but he didn't know what. At the time of the King & Jukes article, I felt that this relationship was a strong argument supporting the prevalence of non-Darwinian evolution. However at the Boston meeting, and in more detail at the Liège Conference on Biochemical Evolution I endeavored to show that this apparent randomness is also to be expected under a panselctionist hypothesis (see the enclosed manuscript, which is to be published in the proceedings of the Liège meeting). (3) The third supporting leg is the apparent constancy of evolutionary rates of homologous proteins in different species. This constancy appears to be very striking but has defied all attempts at rigorous statistical analysis, primarily because one cannot correct accurately for sequential and back mutations, and because the nature of statistical tests are such that one can prove presence of differences but not absence of differences. Besides, the data are peculiar in suggesting that base change mutation rates are constant in time and independent of generation span --- which may very well be the case, but it is a big saving-hypothesis to have to make. Individual exceptions apparently occur, but are they more frequent than expected stochastically? Hard to say. Tom Jukes is also not one to let his past published opinions interfere with his present working opinions. In Jukes' laboratory, Matsubara has sequenced a large part of the ferredoxin molecule of the horse-tail fern and of green algae, with some rather startling results according to Jukes' analysis. Briefly, a synopsis of the differences found in the homologous regions of horsetail fern, flowering plants and green algae: horsetail-alga, 36 base differences; flowering plant-alga, 36 differences; so far so good. But horsetail-flowering plants, 62 base differences. The tree looks like this:



FP = flowering plants

HF = horsetail fern

GA = green alga

CA = common ancestor of land plants.

The difference between contemporary alga and the last common ancestor of land plants is only 5 base differences. There is no way of knowing, at present, how these five base differences are distributed on the two legs leading from the last common ancestor of all three groups. It even seems possible that the modern algal ferredoxin is identical with the ancestral alga ferredoxin of perhaps 600 million years ago.

I regret to say that this work is preliminary and cannot be cited for publication under any circumstances. Otherwise I should probably have used it myself in the Liège paper's discussion of "local adaptive peaks" in protein structure. In sum, I am not at all certain that the apparent constancy of evolutionary rate will continue to hold up.

Incidentally, Dr. Richmond will probably be pleased (or anguished?) to learn that Jukes had already been looking rather intensively into the adaptive significance of the secondary structure of mRNA. Enclosed is a copy of a rough he has sent me on this. Again, the rough cannot be cited yet, but the information that is cited in it is already published.

The fourth leg? I would say that is the Cox & Yanofsky experiment. I can't believe that all of the changes occurring under the greatly increased mutation pressure were adaptive; I can't see how very many if any could have been significantly maladaptive. Dr. Richmond also seems to have stated that he felt that most of the changes may have been neutral. Evolution in the laboratory chemostat is not different in kind from evolution in natural conditions, and it is one of the mathematical verities that the rate of fixation of neutral mutations in a population is equal to the neutral mutation rate in genomes.

However, this is true only of absolutely neutral mutations. Very nearly neutral mutations will also become fixed due to random processes, and here there is some influence of population size. A mutation with a selective disadvantage of less than $1/(2N_e)$ has a reasonable probability of fixation by drift. Obviously the probability that a mutation will be in the range of $0 \pm 1/(2N_e)$ will be a function of N_e . Do not be too cheerful about this; if the apparent constancy of evolutionary rate does not continue to hold up, these considerations offer a plausible out for anyone who wants to believe in the prevalence of non-Darwinian evolution on the basis of other considerations. Actually it is not a very good out, because in order for there to be a prevalence of neutral allele fixations over adaptive allele fixations, it is necessary for neutral mutations (adaptive value less than $+1/(2N_e)$) to be very much more common than even slightly beneficial mutations. It may never be possible to distinguish empirically between completely neutral evolution and very slightly adaptive evolution, and in the end the difference may not be very important. What is important, and seems to me to be becoming increasingly clear, is that one would look in vain to find meaning in every evolutionary amino acid replacement, that there is a large element of chance involved, and that mutation and the patterns of mutation are important driving forces in evolution regardless of whether most changes are neutral, very nearly neutral, or very slightly beneficial.

I have been talking lately to my class about the basic personality and philosophical differences between Th. Dobzhansky and H. J. Muller, and how these traits have carried over into their respective scientific ideas and are still with us -- much to the benefit of science in both cases, let me hasten to add. Muller, intensely creative, trying for decades to create new genes, creating in fact new chromosomes (named after himself); believing in the perfectability of man, and correspondingly in the imperfectness of man, wanting to create a race of superior beings; it was natural for him to think in Platonic terms of perfect genes, and to see all genetic variation as avoidable and lamentable failures of perfection. The concept of genetic load has been an important and

formative idea, an anchor point a backstop, and eventually a convenient target. It was an intensely Mullerian concept, as much as was the idea of freezer banks of near-optimal sperm.

Dobzhansky, on the other hand -- but I don't have to tell you about Dobzhansky! Suffice it to say that you have always and characteristically stressed the intrinsic value of variability, the flexibility of life, and the desirability of life as it is rather than the perfectability of life as it could be. I think it is diagnostic that Muller worked with magical X-ray induced chromosomal rearrangements, while you worked with naturally occurring chromosomal rearrangements.

I am not a Marxist, but I do believe that intellectual progress does arise from the antithesis, synthesis and resolution of conflicting views; that Muller was a better scientist because of Dobzhansky and vice versa. (I hope you don't mind these musings; I am interested in science rather than in personality per se). What do you think Muller would have thought of the idea of neutral mutation in evolution? I rather think he would have found it an unlikely and disagreeable challenge to the platonic ideal of uniquely perfect alleles.

Speaking of famous scientist's personalities and of Marxism, Jukes and I have a specific and pressing problem we'd like you to help us with. We agreed to be American joint editors for a new journal on Biochemical Evolution that Springer-Verlag is going to put out. Now there is a famous Russian scientist, who has recently been considerably honored on the event of his seventieth birthday; Springer would like to bring him in, probably as an editor. Jukes is vehemently opposed to the idea, and I am also opposed, because we have reason to believe that this famous scientist is a Lysenkoist fraud who owes his position principally to political opportunism of the worst kind. I speak of course of Oparin. We are not completely sure of our position -- there is the possibility that the oocervate droplet is a scientifically important concept and that Oparin's work can stand on its merit; that his support of Lysenko in the past was regrettable but forgivable considering the pressures of the times. What do you know of this man, of his work, and of his present political situation? More difficult for us to ask, and most difficult for you to advise us: what is the proper ethical stand? I think Tom is ready to tell Springer-Verlag where to shove their journal and Oparin too.

I have met the man and he seems to me to be something of a boorish tyrant, but perhaps I wouldn't have noticed if I hadn't read Medvedev's book.

Do I understand correctly that you and Francisco are moving permanently to Davis? I hope this wasn't just a fantastic rumor. Welcome to California.

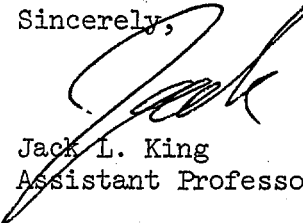
Dr. Th. Dobzhansky

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Francisco: I greatly admire your work on the Lotke-Volterra principle, please send reprints. Could you come to U.C.S.B. for a week or so, and give several lectures? We have a Ford Foundation grant in population biology that would enable us to pay you handsomely.

Sincerely,



Jack L. King
Assistant Professor of Biology

JLK:mt