UNIVERSITY OF OXFORD

DEPARTMENT OF ZOOLOGY

SOUTH PARKS ROAD
OXFORD, OX1 3PS
Telephone: Oxford (0865) 271234
Personal Telephone: (0865)
Fax: (0865) 310447

Prof. H. Sharat Chandra,
Editor, Journal of Genetics,
Indian Academy of Sciences,
C.V. Raman Avenue,
P.B. No. 8005,
Sadashivanagar,
Bangalore 560 080
INDIA

Friday, June 7, 1991

Dear Dr. Chandra,

I am replying to your letter about Dr. Walker's manuscript. I had already been in touch with Dr. Walker (whom I know quite well) about her objections to my citation. I have to admit that I had overlooked her references to outbreeding in the working of her model. The fact is I find her theoretical papers very hard to read and generally have difficulty picking out her central theme. I admit now that I rather dread the task of really trying to follow all that she says in the latest manuscript.

It seems to me that there are probably two themes in her papers referred to, one of which requires outbreeding and the other doesn't. For certain types of gross damage it may be "obvious" to some cellular regulatory mechanism that a piece of DNA script is "corrupt" or "unreadable".† For these types of damage an intact homologue can provide a template for repair. This is the aspect that does not require outbreeding : indeed in principle polyteny with inbreeding would seem a better course for maintaining highly faithful replication. It is, of course, the principle on which microcomputer users work with their disks: keep multiple copies.

† The question of how it is obvious that something needs repair in the genome is an important one and needs to be discussed – I don't think it is in this paper.

If, however, damage is more subtle, so that its effects are only manifest after some organ of the body that is potentially distant from the cells where the damage genes are being expressed (or not being expressed), shows up the bad effects, then there may be no way to eliminate the damage except by letting natural selection take its course. In my opinion natural selectional rectification like this cannot properly be called part of a repair theory of sex. Rather the effect belongs to what I like to call a "mutation clearance by natural selection" theory. For this method of handling damage, outbreeding has great advantages as Kondrashov has shown.

I think Walker's theory includes elements of both processes and hence the confusion. Her overall process improves if *independent* copies of genomes are available because they are unlikely all to be damaged the same way. Undamaged homologues are going to take part in a repair process; but at the same time multiply damaged chromosomes, assembled for elimination by recombination (see Kondrashov), are also being eliminated by natural selection. Without following the theory in detail, I have little doubt the combination of repair and natural selection based on superadditive harm in multiple mutants works well and works all the better under outbreeding rather than inbreeding.

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With this said - that is, that she does have something to grumble about in my over-sweeping linkage of her work with other papers on the repair hypothesis (misguidedly I thought she would be pleased to have *some* reference, because her papers are indeed earlier than the Bernstein et al. paper that later gave prominence to repair and hers are not generally cited) -I have to express a generally negative feeling about the mixture of ideas that makes up the present manuscript. For example the paragraph on p5 about the "50% fitness cost of the maintenance of bisexual reproduction" seems to me to miss the point about cost entirely. She is raising quite a different issue about evolution of a mortal soma. One cannot discuss, still less dismiss, the issue most of us are concerned about without any reference to maleness, male functions, anisogamy, etc. because it is only these characteristics of sexuality that raise the problem.

For the rest there is a lot that, as usual, I cannot follow, but I gather again a generally negative impression from phrases like 'the whole genome is the target of selection', 'part and parcel of a changing concept', 'much of what was formerly believed to be the result of random events is recognised as high precision mechanics'. I see these as expressions of a drive in her thinking about evolution (all too common generally) which believes neo-Darwinism to be outdated, but takes this view without any substantive new theory to replace it and instead a lot of fuss about neo-Darwinism's supposed difficulty with minor details. However, I suspect that my own strong adherence to the older paradigm also reflects bias of my own; therefore I very much hope you are getting this paper also reviewed by someone else who is likely to have more appetite for all of the details she does discuss.

In summary, it is a paper I find hard to judge because of my own biases and because of a seeming incompatibility in our approaches to theory. My impression is of a rather diffuse presentation. It certainly includes some misunderstandings about "classical" theory - e.g. the one about what classical theory sees as the cost of sexuality. More weight, however, should be given to reports of referees more familiar with Dr. Walker's type of subject matter.*

If you and/or Dr. Walker should wish it I would be happy to publish in Journal of Genetics a one-paragraph retraction of my lumping of her theory with this repair philosophy. This retraction would summarise what I say in the opening paragraphs of this letter.

Yours sincerely,

W D Hamilton

Prof. W. D. Hamilton, FRS

* Possibly yourself – or someone in your group??