Tl. note

2/17/90

The concept of the gene: from atom to molecule.
A tinge of Lamarckism
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"Gene" was defined as an indivisible element of heredity -- as an "atom". Nevertheless the history of genetics has been tinged by many controversies about the responsiveness of genes to environmental influence. Most claims of specific adaptive responsiveness have been repudiated. Natural selection has been shown to be a source of creative molding of biological outcomes in systems as diverse as drug resistance in bacteria and antibody formation in mammals.

Now that genes are known to be DNA molecules, we can approach the constraints on possible adaptive directed mutation with more precise chemical insight. In particular, the classical trinitarian dogma, DNA => RNA => protein is complicated by a myriad of feedback mechanisms, with DNA-binding proteins playing a complicated role in the regulation of gene expression. Further, DNA-methylation is also implicated in that regulation. In turn, these may cause or interact with a wide range of conformational distortions, bends, loops, supercoiling and unravelling, Z-DNA; in a few cases these DBP's have important enzymatic effects: topoisomerase, gyrase. In special circumstances, phase variation and some terminal differentiations, DBP's are site-specific recombinases. In vitro, DBP's may protect DNA sequences from attack by endonuclease-1; at the same time, gene activity is associated with vulnerability to this enzyme.

Furthermore, RNA information may reenter the DNA genome by reverse-transcription. I expect RNA segments to be found to play a role in gene expression by site-specific binding to DNA, though I have not yet encountered an example. It will be surprizing if some ribozymes do not attack DNA (as well as RNA).

RNA's and their protein products are themselves environmentally regulated, mainly at the transcriptional level. This is an indispensable core of physiological adaptation of cells to their environment.

Given all the above it is hypothetically likely that mechanisms will be found whereby the local STABILITY of a gene region will vary according to the environment, and in particular the transcriptional regulatory status of those genes. This would be atop less specific changes of mutability under stress (SOS reaction). If not closely studied, this regional destabilization would simulate a "lamarckian*" process, for a higher local mutation rate would enhance the likelihood that some adaptive mutations occurred (whilst the majority were the contrary.) It would be a good strategy for organisms to become locally unstable when confronted with substrates that could initiate but not consummate a transcriptional process. The existing transcriptional controls offer a range of chemical sensors; it would be gratuitous to invoke others.

I have been led to this enquiry by John Cairns' experiments; but I find them [so far] unpersuasive. His theoretical models are a subset of those implied by the foregoing

"*" not quite accurate to attribute to Lamarck!

discussion. B. D. Davis' ideas are very close to my own [v. infra]. There is a small handful of in vivo experiments to support the general views expressed here -- I would welcome hearing of others -- I hear some may be in the mill.

1. Mellon and Hanawalt -- have shown that UV photoinduced thymine dimers are preferentaīlly repaired in the transcribed strand both in eukaryotes and in bacteria. This amounts to a protection against mutation under transcription; but there has been no more general study comparing the initial dimerization reactions with and without induction. This work is very recent.

2. Kohno and Roth have reported a pronounced (10 - 100x) increase in the yield of proflavine-induced mutants after induction of transcription. Though this work dates to 1974 I have seen very little comment on it. (I thank Phil Leder for calling it to my attention).

3. On a cognate matter, Yokota et al. have reported a tissue-specific DNA alteration in mouse brain; so similar phenomena may indeed play a role in epigenesis (beyond the site-specific recombinases involved in immunoglobulin diversification.)

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(4) Kohno-T and Roth-J 1974 J Mol Biol 89: 17-32.
Proflavin mutagenesis of bacteria

(5) Davis-BD Transcriptional Bias - A Non-Lamarckian Mechanism for Substrate- Induced Mutations Proceedings of the National Academy of Sciences of the United States of America 86: (13) :5005-5009 (1989)

(6) Yokota H; Iwasaki T; Takahashi M; Oishi M A Tissue-Specific Change in Repetitive DNA in Rats Proceedings of the National Academy of Sciences of the United States of America, 86, (23): 9233-9237 (1989)

I append Davis' and my bibliography; if you know of still other pertinent works, I would welcome hearing about them.

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