Quantum Indeterminism and Evolutionary Biology*

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In "The Indeterministic Character of Evolutionary Theory: No 'Hidden Variables Proof' But No Room for Determinism Either," Brandon and Carson (1996) argue that evolutionary theory is statistical because the processes it describes are fundamentally statistical. In "Is Indeterminism the Source of the Statistical Character of Evolutionary Theory?" Graves, Horan, and Rosenberg (1999) argue in reply that the processes of evolutionary biology are fundamentally deterministic and that the statistical character of evolutionary theory is explained by epistemological rather than ontological considerations. In this paper I focus on the topic of mutation. By focusing on some of the theory and research on this topic from early to late, I show how quantum indeterminism hooks up to point mutations (via tautomeric shifts, proton tunneling, and aqueous thermal motion). I conclude with a few thoughts on some of the wider implications of this topic.

1. Introduction. What effect, if any, does quantum indeterminism have on the processes of evolution, and should it make a difference either way to modern evolutionary theory? This question is related to the older question of whether biology, including evolutionary biology, is reducible to physics (or rather physics and chemistry). But that is not my central concern here. It is generally agreed that evolutionary theory inherently involves probabilities and statistics (I use these words interchangeably). But what is the *source* of the statistical character of evolutionary theory? Brandon and

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Carson (1996), in explicit opposition to Rosenberg (1988, 1994) and Horan (1994), locate the source in some of the processes involved in evolution, namely point mutations with a basis in quantum indeterminism, genetic drift, and natural selection (which they argue is inextricably linked in real life with drift), the first being reductionistic, the latter two being autonomous to biology. In reply to Brandon and Carson, Graves, Horan, and Rosenberg (1999) attempt to refute their arguments one by one, focusing on each of the three processes listed above. Their position involves not only a strong leaning toward a deterministic interpretation of the processes in evolution (determinism = [every event requires a cause] + [same cause, same effect]), but more importantly they locate the source of the statistical character of evolutionary theory in the (necessary) epistemic limitations of biologists.

In this paper I focus only on the issue of point mutations with a basis in quantum indeterminism. This is an important and relatively unappreciated topic. The case made by Brandon and Carson for quantum indeterminism "percolating up" to the level of DNA mutations, and therefore phenotypic traits, suffers from ignoring the topic of possible mechanisms, while the reply by Graves et al. is misconceived in the extreme.

2. Preliminary Criticisms. Brandon and Carson provide a hypothetical example where a haploid population has two alleles for a particular gene. A frequency of 1 or 0 for either allele is stable in this population, but it so happens that the frequency of each allele is .5, which is unstable. With such a situation a point mutation that turns one of the alleles into the other would result in a push by natural selection toward a frequency of 0 and 1 respectively. Thus if that pivotal point mutation was the result of a quantum indeterministic event, then "quantum uncertainty would 'percolate up' in a powerful way to the level of populations" and "The evolutionary trajectory of such populations would be genuinely indeterministic." (320)

Graves et al. argue that this scenario is highly unlikely. They believe that quantum indeterminism, involving genuine ontological chance, is limited to the micro-level to such a high degree that it is not worth taking into consideration at the level of biological processes, including evolutionary processes. They concede that "it is not in principle impossible that quantum indeterminacy might occasionally alter a biological outcome." However, they believe that the odds are "overwhelmingly improbable," or as they prefer to put it "the odds asymptotically approach zero." (145) Although their arguments are stated much too briefly for my liking, they are as follows (144–145): Brandon and Carson's scenario requires that "a single point mutation . . . will result in the nuclear material which codes for the product of the *A* allele now switching to code for the *a* allele." This

is "overwhelmingly improbable" because of the following factors: (1) "The changes required to mutate [one DNA base into another] . . . would be quite considerable, clearly involving a substantial aggregation of micro-processes," (2) "the size of the smallest genes," (3) "the redundancy in the [genetic] code," (4) "the relatively small effect of amino acid substitutions in homologous proteins," and (5) "the possibility of additional 'random' events occurring to offset the point mutation."

In reply to these five points I shall begin with the last and proceed toward the first. The first seems to me the most serious in terms of error, but because it touches on the most profound issue in this topic I have saved it for a separate section. Beginning with the fifth criticism above, then, it is always possible that a point mutation, granting for the sake of argument a quantum indeterministic cause, could be canceled out by "additional random events." Graves et al. do not elaborate on what they mean by this latter phrase, but there are basically two scenarios that could satisfy their claim. One possibility is what is known as a back (or reverse) mutation, a mutation (not necessarily in the same codon) that restores the function of a gene lost by an earlier mutation in that gene. In the scenario envisioned by Brandon and Carson, it is possible that the pivotal point mutation which started the teetering effect could be canceled out by a back mutation, preferably early in the resulting DNA lineage, thus stopping the teetering effect begun by the first mutation. But the odds of this are quite low. As Futuyma (1998, 272) points out, back mutations "occur at a much lower rate than 'forward' mutations from wild type to mutant, presumably because many more substitutions can impair gene function than can restore it." A second possibility is that another organism in the same population could experience at a close enough time a mutation in the same locus but in the opposite direction, thus offsetting the teetering effect. But given the relative infrequency of mutations (which I shall look at more closely later), the probability of this latter scenario is again so low as not to merit consideration. Either way, then, these slim possibilities do not negate the force of randomness in Brandon and Carson's original scenario.

The fourth point by Graves et al. concerns amino acid substitutions in homologous proteins. By "homologous proteins" I presume they are referring to proteins, whether in closely or distantly related species, that are not merely similar but are similar because of common descent. Their point seems to be that many amino acid substitutions in such proteins result in little if any difference in function. If this is what they are saying, it is certainly true. But they still do not have a strong point. It all depends on the nature of the protein, the site of the substitution, the kind of amino acid substitution, and the importance of that site for the functioning of the protein. Accordingly in many proteins all it takes is one amino acid substitution to significantly compromise the functioning of that protein

(and thus result in a different allele), resulting in lower fitness or even death, and of course sometimes but much less frequently in higher fitness. The classic example is the hemoglobin protein and the case of sickle-cell anemia. A single nucleotide substitution of adenine for thymine in the second position of the codon that codes for the sixth amino acid in the 146 amino acid long β chain results in valine in that position instead of glutamic acid. This in turn results in red blood cells that take on a sickle shape, resulting in severe anemia and death when the mutated gene is homozygous. In persons where the gene is heterozygous, the anemia is only mildly disabling and the heterozygotes are actually fitter in places with malaria than the normal homozygotes (with normal hemoglobin) because of the degree of immunity their condition confers against that disease.

Since for any one species, let alone for all living species, molecular biology is very far from determining the effect in protein functioning of every possible amino acid substitution resulting from point mutations, it is impossible at this point in history to provide an estimate for the total ratio between functionally indifferent and functionally different amino acid substitutions. Nevertheless one cannot help but be impressed by the ever-growing caseload of discoveries wherein a single point mutation results in a differently functioning protein, as well as by the nature of each case. Typical is the discovery of Fardella et al. (1994) that a single point mutation from G (CGC) to A (CAC) in codon 440 of the P450c17 gene results in the substitution of histidine for arginine, which results in 17α-hydroxylase deficiency and an ensuing total lack in pubertal development in both genetic sexes. Previous mutation studies on the same gene resulting in the same deficiency led the above authors to conclude that "the activity of P450c17 is very sensitive to minor changes in its structure." (163)

But the basic problem with the fourth point of Graves et al. is that the typical textbook comparison of homologous proteins is, by necessity, focused only on examples of amino acid substitutions that have been evolutionarily successful. For example, Freeman and Herron (1998, 61) point out that the amino acid sequences in two sections of a protein involved in eye development are over 90% identical between humans, mice, rats, quail, zebrafish, and fruit flies. What such examples by their very nature overlook are the much more numerous *dys*functional proteins that must have arisen and were selected against during the phylogenetic history of each of these (groups of) species.

The third point by Graves et al., referring to the synonymy of the genetic code, although of course true, does little to affect the position they are attacking. The genetic code is the specific mapping of 64 codons to 20 amino acids, with each codon coding for only one amino acid. There is thus significant synonymy (a.k.a. redundancy, degeneracy) in the code. It

so happens that three amino acids are each coded for by six codons, five by four codons, one by three codons, ten by two codons, and two by one codon (leaving three codons that code for no amino acids whatsoever but serve instead merely as stop codons). Almost all of the synonymy occurs in the third position of the codons. Graur and Li (2000, 28) provide the following breakdown (which does not include stop codons): of the possible substitutions in the third position of the codons, 69% are synonymous; of the second position, 0% are synonymous; of the first position, 4% are synonymous. Thus, of all possible nucleotide substitutions, only 25% are synonymous (i.e., silent). Fully 75% make a difference (providing we are talking about coding regions). Even granting that some sites seem to have different mutation rates (Graur and Li 2000, 35–38), the general ratio of silent to nonsilent mutations (1:3) is certainly much too low for the criticism of Graves et al. to have any force.

The second point by Graves et al. refers to the size of genes, such that (presumably) the number of bases of relatively small genes (let alone large genes) is too large for spontaneous mutations to have anything but a negligible effect. Of course Darwin himself stressed *small* changes in cumulative selection. And although he was referring to small changes in the phenotype, his approach readily translates to the genotype via micromutations and is central to neo-Darwinism. But more to the point, we have already seen in the cases of hemoglobin and P450c17 how a nucleotide substitution at a single site can have a profound difference on the phenotype. And of course the number of known examples is large and growing all the time. Thus even with small genes one should expect that sometimes a single point mutation will have a significant phenotypic effect. And this only becomes amplified as one deals with larger genes, since these generally have more opportunities for mutations.

There's nothing like focusing on humans to get this point across. The average length of a human gene is maybe 3,000 base pairs. This does not stop mutations from being significant in human evolution. The current consensus is that humans have at least 100,000 functional genes. Granting the current estimate that the average gene undergoes 10^{-5} phenotypically detectable point mutations per DNA generation (which of course underrepresents the actual amount of point mutations), it follows, as Futuyma (1998, 274) points out, that

> *almost every gamete carries a new, phenotypically detectable mutation somewhere in its genome* (10^{-5} mutations per gene $\times$ 10^{5} genes $=$ 1 mutation per haploid genome in humans). So in a population of 500,000 individuals, about one million new mutations arise every generation. If even a tiny fraction of these were advantageous, the amount of new "raw material" for adaptation would be substantial, especially

> over the course of thousands or millions of years. These figures may be underestimates, for at the molecular level, each human haploid genome may carry about 200 new nucleotide substitutions.

Add to this the fact that the average adult human is composed of roughly 10 trillion cells, and the picture for the evolutionary biology of humans becomes even more significant, given the relation between mutation and disease (i.e., it's not just the germ line that counts when it comes to evolution).

3. The Long and Winding Road From Copenhagen to Cambridge. Finally I turn to the first argument by Graves et al. They ask us to "Consider the shape and complexity of an adenosine [sic] molecule." That being done (for adenine), they tell us that

> The changes required to mutate this molecule into a guanine molecule would be quite considerable, clearly involving a substantial aggregation of micro-processes. Because the outcome of micro-events aggregating to this extent is asymptotically deterministic at even the level of macro-physical processes, BC's [Brandon and Carson's] assertion that the processes creating point mutations are indeterministic is an assumption very much in need of defense. (144 n. 7)

Granted, Brandon and Carson did not address how a quantum event might result in a point mutation. But the real error belongs to Graves et al. First, except in the case of *induced* mutations by chemical agents and ionizing radiation, where methylation, for example, can cause a guanine to behave like an adenine during subsequent replications (cf. Drake et al. 1983, 215), molecular biologists on the topic of *spontaneous* point mutations (mutations with no outside causes) never talk about one DNA base mutating into another, not, at least, as the result of a single micro-event let alone a "substantial aggregation" of such. Rather their claim is that a spontaneous point mutation occurs with the *placement* of the wrong base during DNA replication (hence phrases such as "copying error," "base substitution," "base mismatch," etc.).

The problem still remains, however, of how a quantum event, a micro-event of pure chance, might result in a point mutation and hence affect the course of biological evolution. If the debate between Brandon and Carson on the one hand and Graves et al. on the other is to be resolved, the answer to this problem must be found and elucidated. But this is no easy task, for the topic is cross-disciplinary and scientists are specialists who in their publications typically focus on parochial tasks. Nevertheless there is a history of important and interesting work on our subject, especially from the past decade, which establishes a number of mechanisms,

all of which philosophers would be wise to be aware of. This history overtly begins in Cambridge, but to understand that beginning and what happened afterward we need to go back earlier to what began in Copenhagen.

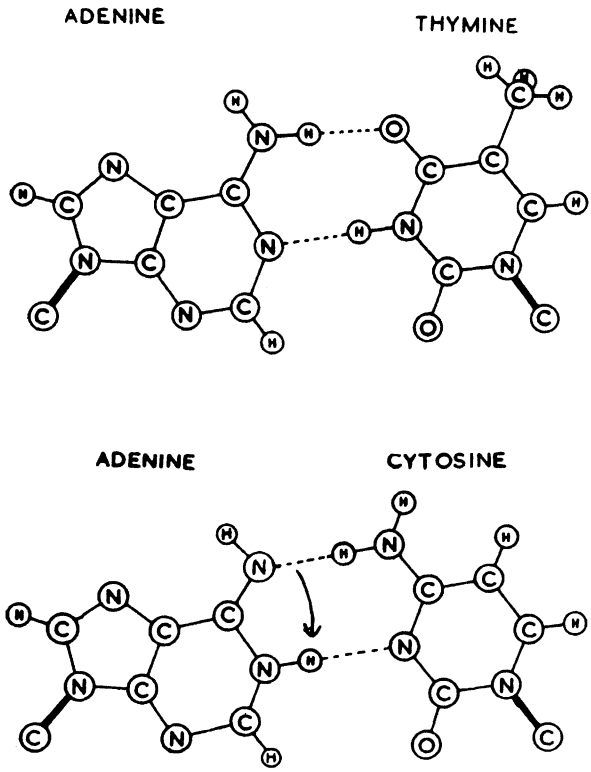
3.1. Quantum Indeterminism. The laws of quantum physics are statistical, not classical. Originally quantum physics was largely inspired by a positivist theory of meaning, such that it was not false but meaningless to make pronouncements about phenomena that are in principle unobservable. Accordingly it was meaningless to say that an electron has both position and momentum, since one could measure only one or the other but not both simultaneously. Similarly it was meaningless to say that an electron has a path inside an atom, even though the path of an electron could be measured in a cloud chamber. This was the Copenhagen interpretation of quantum physics, developed by Niels Bohr, Max Born, and further extended by Werner Heisenberg (cf. Heisenberg 1989, chs. 3, 4, and 7).

Some physicists, such as Einstein, thought that behind the statistical phenomena there must be deterministic certainties, so-called hidden variables that, if known, would explain where the probabilities come from. But this view grew less popular as time progressed. In recent decades, due especially to two experiments conducted in Paris in the early 1980s by Alain Aspect and his colleagues (which proved conclusively that quantum probabilities are correlated non-locally), there has developed an overwhelming consensus among physicists that the deterministic hidden variables interpretation of the quantum world is inappropriate and that a view rooted in the traditional Copenhagen interpretation must be accepted (Rohrlich 1983), specifically a view according to which the quantum world is fundamentally statistical, with genuine ontological chance. Accordingly quantum phenomena such as radioactive decay came to be thought of as irreducibly statistical, with individual atoms of a radioactive element decaying at random, but *en masse* within a precisely determined time (the half life). Similarly an electron in an atom is no longer thought to be a particle orbiting a nucleus, but rather a cloud of probabilities (its wave function) constrained within a certain region (its orbital), a cloud moreover that is subject to random energy fluctuations and discrete quantum jumps from one quantum orbital to another. In recent years it has even become possible to study a free electron, for months, in what is known as a Penning trap. As Charles Enz (1999, 220) put it, "The electron oscillates in the trap and makes random quantum jumps which are caused by the coupling of the electron's charge to the ever present *electromagnetic vacuum fluctuations*." In all of this, quantum physics has outgrown the now outdated positivism with which it began (cf. Weinberg 1994, 174–

184). In accepting the accumulated evidence for the wave nature of the electron, and indeed of other particles and even (as recently discovered) of whole atoms, quantum physics has settled on a view of the quantum world as fundamentally statistical in nature.

3.2. Tautomeric Shifts. The connection between mutations in biology and quantum indeterminism has a pedigree that goes back to the early 1930s, specifically to the work of Max Delbrück, which in turn was further elaborated and made famous in Erwin Schrödinger's 1944 book *What is Life?* In Chapters 4 and 5 of that book Schrödinger speculates that a mutation in genetics (a new allele in the same locus) is caused by a random "quantum jump" resulting in a rare but stable "isomeric transition" in the gene. These mutations would be relatively rare because of the unusually high energy threshold that needs to be reached by the quantum jump. As an example of such an isomeric transition, Schrödinger uses two kinds of propol-alcohol, in which an oxygen atom, situated between a carbon atom and a hydrogen atom, breaks its bonds and migrates (via a number of intermediate steps) to a different part of the molecule, resulting in a different, but equally stable, molecule. Interestingly, Schrödinger strongly suggests in the final chapter of his book that beyond such mutations quantum indeterminism has no relevance to biology.

Obviously influenced by the Delbrück/Schrödinger model of mutation, Watson and Crick (1953), while working in the Cavendish Laboratory at Cambridge, suggested a model of mutation that quickly became a paradigm. On the topic of DNA replication they speculated that "while adenine will normally pair with thymine, if there is a tautomeric shift of one of its hydrogen atoms it can pair with cytosine. The next time pairing occurs, the adenine (having resumed its more usual tautomeric form) will pair with thymine, but the cytosine will pair with guanine, and so a change in the sequence of bases will have occurred." (272) Later the molecular biologist and Nobel laureate Jacques Monod (1971, 192), in his classic on chance and evolution, would claim factual status for this model. The model works as follows. Tautomeric shifts are easily reversible isomeric shifts. The major tautomeric form of a DNA base is a relatively stable state of chemical equilibrium. That equilibrium can occasionally be temporarily offset resulting in a minor tautomeric form. This occurs when one of the hydrogen atoms migrates to another place on the molecule. The temporary migration of the hydrogen atom results in a different bonding configuration for that DNA base, so that, as Watson and Crick suggested, during DNA replication an adenine molecule will pair with a cytosine molecule instead of a thymine molecule, or as Monod suggested a cytosine molecule will pair with an adenine molecule instead of a guanine molecule. The following illustration is from Watson and Crick (1953):



The key to this model is the change in configuration of the hydrogen bonds (represented above by dotted lines). In the double helix, adenine and thymine are connected together stereochemically by two hydrogen bonds, guanine and cytosine by three hydrogen bonds. In each of the four bases, their hydrogen atoms have their preferred locations. If this were not so, as Watson et al. (1987, 242) point out, "then DNA could not function as a genetic molecule, for it is the complementary relationship between opposing chain sequences that gives DNA its capacity for self-replication." When one of the four DNA bases temporarily assumes one of its minor tautomeric forms, because of the migration of a hydrogen atom, it can no longer bond with its corresponding base, but will bond with a different base. Adenine and guanine are purines, thymine and cytosine are pyrimidines. In addition to purine-pyrimidine mismatches (A*:C, A:C*, G*:T, and G:T*, where the asterisk denotes a minor tautomeric form), in the mid 1970s it was found that purine-purine mismatches can also occur (A*:A, A*:G, G*:A, and G*:G), although pyrimidine-pyrimidine mismatches were found to be impossible. At any

rate, all of these mismatches must be quite rare, otherwise, to quote Watson et al. again, "the many errors (mutations) incurred during DNA replication would be incompatible with orderly cell growth and division." (243)

Since the 1970s, the topic has become much more complicated. Drake (1991, 126–128) points out that, as a result of structural studies using both X-ray crystallographic and nuclear magnetic resonance (NMR) techniques, further models of base mismatches have proliferated. For example, in the early 1980s many different models of misalignment between G:C and T:A in their major tautomeric forms were developed, some of them to explain frameshift mutations, while in the late 1980s it was found that pyrimidine-pyrimidine mismatches sometimes occur: T:T, C:C, and T:C, with an H_2O molecule functioning as a bridge between the T:C mismatch.

The situation has gone so far that von Borstel (1994, 132) argues that although tautomeric shifts are appealing in theory and are still used as a major model for point mutations in undergraduate textbooks, "data do not exist which indicate that . . . tautomeric shifts have ever been responsible for even one spontaneous mutation of any kind. Certainly, the rare tautomer does not *persist* in the double helix and without its persistence, its effect on mutation production is a mirage."[1] What the recent experimental evidence does support is summarized in von Borstel's paper, namely: (1) Wobble: although guanine and cytosine typically involve three hydrogen bonds, guanine can sometimes pair with thymine using only two hydrogen bonds (similarly for cytosine with adenine). Such wobble pairs are misalignments involving major tautomers. (2) Bond angles: changes in angle of at least one of the hydrogen bonds can sometimes result in different base pairs. (3) Protonation: the addition of a proton, usually to a ring nitrogen, results in an ionized form of the base (sometimes stable), and hence in a different bonding configuration (similar to a minor tautomer but without tautomerization).[2] (4) Transient misalignment and dislocation: occasionally during DNA synthesis a base in the single-stranded template will temporarily swing backward, thus failing to receive a com-

1. It would seem that von Borstel's demand for persistence is too strong. As Drake et al. (1983, 214) point out, "Although such base tautomers are rare and short-lived, they may produce mutations when they occur at the moment of base addition to the growing chain." I shall provide supporting evidence for this below.

2. Sometimes this can be combined with wobble, as with a protonated adenine in an A^+:C wobble mismatch. Cf. Hunter and Brown (1999) for over 20 diagrams, each a different configuration of hydrogen bonding between base pairs and altered base pairs, including one that involves four hydrogen bonds between them. In addition, von Borstel's (1994) diagrams include an A:C wobble with only one hydrogen bond. Interestingly, Lavery and Zakrzewska (1999, 45) claim that "The present state of knowledge . . . suggests point mutations occur most frequently as a result of the formation of G:T and A^+:C wobble pairs rather than of tautomeric forms. This is supported by an increasing number of crystallographic structures containing mispairs."

plementary base, but will then swing forward, pairing with the base previously paired with its neighbor, which will then receive a new complementary base. The base that temporarily swung backward might therefore now be paired with a non-complementary base.

None of these models involve rare tautomeric forms. The reason why the standard Watson-Crick model of tautomeric shifts has become largely disfavored in recent years by many molecular biologists, though never discounted as a possibility in reality, is that because of their rarity and brevity during the replication process they can never be observed experimentally. (Hunter and Brown 1999, 315) Hence other models, amenable to experimental evidence, have proliferated, with a backlash of criticism by those who favor the traditional paradigm. In addition to the models discussed by Drake (1991) and von Borstel (1994), models using base-pair analogs have become quite common. Fagan et al. (1996), for example, used NMR spectroscopy to explore the role of 2-aminopurine (AP), a highly mutagenic analog of adenine, and found that in two different DNA sequences the AP:C mispair was in a wobble geometry at both neutral and high pH, and that its stability was dependent upon the local base sequence. Moran et al. (1997) claim that 2,4-difluorotoluene, a base analog of thymine, is non-polar and incapable of forming hydrogen bonds, nevertheless DNA polymerase readily binds it to adenine, so that conventional hydrogen bonds may not be necessary for high efficiency and fidelity during DNA synthesis. Instead they claim that geometry (size and shape of the molecule) is probably the most important (and perhaps even the only) factor (cf. Goodman 1999 for further support). In reply, Evans and Seddon (1997) claim to have experimentally demonstrated that 2,4-difluorotoluene is both polar and capable of hydrogen bonds, thus reaffirming the importance of hydrogen bonds for replication fidelity and defending the *status quo*. Moreover, since the minor tautomeric forms of the standard Watson-Crick base pairs are too infrequent (1 in 10^4–10^5) and too short-lived for experimental study, a number of researchers (e.g. Fazakerley et al. 1993; Robinson et al. 1998; Suen et al. 1999) have used base analogs and synthetic bases, both with much greater frequencies of minor tautomerism, to experimentally study their role in mutagenesis, with positive results, thus reaffirming the roles of hydrogen bonds and tautomeric shifts.

Whatever the truth given the above situation, it has become clear that a wide variety of possibilities exist for base-pair mismatches in DNA, both experimentally confirmed and legitimately hypothesized. Moreover the uncertainty in the current state of the science necessitates that all of the above possibilities, including tautomeric shifts (as well as quantum tunneling, to be discussed below), have to be taken seriously if we are to explore how quantum indeterminism can hook up to spontaneous point mutations.

In the case of tautomeric shifts, Monod (1971), though not the first, famously connected them to quantum indeterminism via "quantum perturbations" (111), such that "A mutation is in itself a microscopic event, a quantum event, to which the principle of uncertainty consequently applies. An event which is hence and by its very nature *essentially* unpredictable." (114–115)

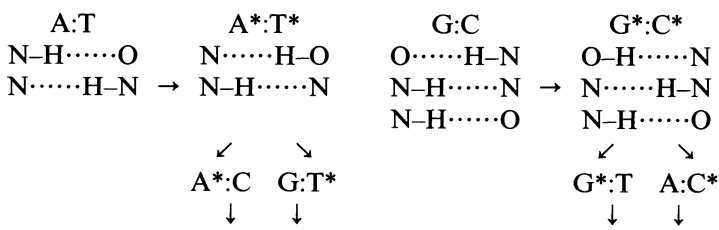
How stands this viewpoint today? As we have seen, mutations by tautomeric shifts have thus far remained beyond the pale of direct experimental confirmation. Nevertheless the Watson-Crick model has remained a viable model, connected to quantum indeterminism via quantum jumps, and has only become more interesting with time. Kwiatkowski et al. (1986) review the experimental evidence for the conclusion that minor base tautomers occur in aqueous solution on a ratio of 1 in 10^4–10^5, as well as the difficulties involved in estimating the threshold energies required for the relevant quantum jumps, which nevertheless are estimated to be roughly 6–8 kcal/mol (125).[3] Nothing has happened since 1986 to significantly change these estimates. (Kwiatkowski, pers. comm.)

But more interestingly, Kwiatkowski et al. (1986) also review the then fairly recent evidence that the ratio of minor to major base tautomers when isolated in an inert gas is roughly equal, having roughly the same intrinsic stability. Given more recent discoveries concerning the structure and function of DNA polymerase (the enzyme responsible for pairing nucleotides and their bases during DNA synthesis), this has interesting consequences for the role of minor tautomeric forms in spontaneous base mutations. Poltev et al. (1996, 723) conclude from the above difference in ratios (inert gas vs. aqueous medium) that "hydration should be the main, if not the only, source of the preference for the keto [major] tautomer in aqueous solutions." Doublié and Ellenberger (1998, 708) point out that at the replication fork, when the DNA polymerase is fitting the nucleotide opposite the template base, "More than 90% of the surface of the base pair is buried from [the aqueous] solvent." All of this suggests that a minor tautomer while grasped in the "hand" of the DNA polymerase (cf. the diagram in Doublié and Ellenberger 1998, 704) can remain stable long enough (because it is no longer in an aqueous solution) for insertion opposite the template base. Of course it must be added that the models for spontaneous point mutations have become so numerous, given the variety of known and possible mechanisms, that a quantitative or even a semi-quantitative estimate

3. This is roughly equal to 0.26–0.35 electron volts (1 kcal/mol = 0.04336 eV). Interestingly, this is close to, albeit somewhat lower than, Schrödinger's (1944, 63) estimate for the range of threshold energies at which quantum jumps can affect an isomeric transition in propyl-alcohol, namely 0.9–1.8 electron-volts.

for the role of Watson-Crick tautomeric shifts is not possible, and the literature, both early and recent, repeatedly reflects this conclusion.

3.3. Proton Tunneling. Interestingly, the incorporation of minor tautomers by DNA polymerase during DNA replication is not the only model of spontaneous point mutation by tautomerization. Another model involves quantum tunneling, a well-known statistical phenomenon in which a quantum particle can sometimes penetrate a barrier, such as an electron barrier surrounding an atomic nucleus. This is possible because a particle in quantum physics is not conceived classically but rather as a "wave packet" which obeys the probability laws of quantum theory. Löwdin (1965) was the first to develop in detail a theory of spontaneous point mutation caused initially by tautomerization within the double helix, not involving the existence of free rare tautomers in the aqueous environment. Explicitly using the quantum mechanical concept of a "quantum jump" (222), he argued that occasionally a proton (hydrogen atom) could tunnel through one of the hydrogen bonds between two complementary base pairs in DNA. Since each of the canonical bases has a neutral charge, he argued that such a proton transfer would almost certainly cause a simultaneous anti-parallel proton transfer through another hydrogen bond in the base pair so as to keep the charges neutral. Since the bases are protected from the aqueous medium, the newly formed minor tautomers would remain in their minor state for much longer than minor tautomers in the aqueous medium. Hence the minor tautomers could sometimes be involved in DNA replication, causing mutations. His model can be illustrated as follows:



Löwdin speculated that, in each hydrogen bond between the bases, there must be what he called a "double-well potential." Each double well must be highly asymmetrical, with the threshold energy from A:T to A*:T*, and G:C to G*:C*, being much higher than the reverse so as to allow for the stability of the genetic code. Assuming that the original minor tautomers remain in their state long enough, they can be immortalized through subsequent replications. However, at some stage the minor tautomers are likely to revert to their major form, so that eventually A:T → G:C and

G:C → A:T. Löwdin also speculated that a single proton could tunnel between complementary pairs. This would most likely occur as the result of exposure to a mutagen such as ionizing radiation, and would lead to pairs such as A^-:T^+ or G^+:C^-. If any of these ionized tautomers were to remain ionized at the time of DNA replication, it would be unlikely that they could pair with a neutral canonical base. The result would therefore probably be a frameshift mutation in the form of a deletion.

Löwdin (1965) offered his theory as a plausible addition to the Watson-Crick model of tautomeric shifts, recognizing at the same time (333–334) that it was impossible to say which model accounted for more mutations. Since its inception, there have been two main obstacles preventing general acceptance of Löwdin's theory. The first concerns the precise nature of hydrogen bonds. Löwdin's theory explicitly depends on Linus Pauling's model. (Löwdin 1969) In the 1930s Pauling argued that the hydrogen bond is partly covalent, involving significantly overlapping wave functions. Although his model has long remained a popular one, many have argued against it, in favor of an essentially electrostatic model. The second obstacle for Löwdin's theory involves the lack of experimental evidence for proton tunneling within base pairs.

Interestingly, both of these concerns have only recently been settled, and in a manner highly favorable to Löwdin's theory. In the case of the hydrogen bond, in 1998 an experiment conducted in Grenoble established that the hydrogen bond in ice is roughly 10% covalent, the rest being electrostatic. Of course further experiments await, especially with regard to water, but already a partially covalent picture of hydrogen bonds is required to explain the unusual properties of water. (Martin and Derewenda 1999)

As for experimental evidence for proton tunneling within base pairs, it is only with the application of a variety of recent experimental and computational techniques that Löwdin's basic theory has enjoyed a revival. Perhaps the most important work here is that of Florián and Leszczyński (1996). Focusing on the G:C pair, they point out that there are only two possibilities for double proton transfer wherein the base charges remain neutral, and they argue that one of them is so unlikely that it is not worth consideration. The one that is worth consideration is the G*:C* pair in my diagram above. The energy threshold for the transition from G:C to G*:C* they calculate to be 14.6 kcal/mol, while the energy threshold for the reverse transition they calculate to be 5 kcal/mol. Based on these energy thresholds, they estimate the ratio of G*:C* to G:C in DNA to be 1 in 10^6–10^9, which they point out is of obvious significance for the topic of spontaneous mutation. The energy threshold for the transition from A:T to A*:T* they calculate to be 16.6 kcal/mol. From this they estimate the ratio of A:T to A*:T* in DNA to be 1 in 10^{12}, which, they point out,

eliminates this part of Löwdin's theory as a probable cause for spontaneous mutation.

Naturally, Florián and Leszczyński's results cannot be disentangled from competing models, so that one cannot say which has more application to reality.[4] Nevertheless it is interesting to note that their results go far to explain the different mutation percentages contributed by each of the four canonical bases, summarized by Graur and Li (2000, 126) as A: 20.3%, T: 20.4%, C: 29.5%, G: 29:7%. Although Graur and Li offer no explanation for these percentages, the results of Florián and Leszczyński help explain why cytosine and guanine are involved in more mutations.

3.4. Thermal Motion. The above two main models of tautomeric shifts are not the end of the story for how quantum indeterminism hooks up to point mutations. As we have seen earlier, the Watson-Crick model of tautomeric shifts has come under attack in recent years (the proton tunneling model is usually overlooked) in favor of a number of different models. The issue is whether DNA polymerase "recognizes" which base to pair to the template base based on hydrogen bonds or on geometry. Currently no one knows for sure (Fagan et al. 1996, 4026; Doublié and Ellenberger 1998, 708), although both factors may be important. (Drake, pers. comm.) According to the geometry view, hydrogen bonding is not the key to recognition but only follows (if at all) after the base (whatever it is) is inserted, and if the fit is not right (based on the standard Watson-Crick geometry) then the repair enzymes will come into play. The debate is an example of good science, and it will be interesting to follow it over the coming years. As things are now, however, the competing models only open up more possibilities for how quantum indeterminism might hook up to evolutionary biology.

To see how this is so, we need to consider a little more closely the action of DNA polymerase. Operating at the replication fork, DNA polymerase connects one nucleotide at a time, based on the single-stranded template. It is estimated that it connects between 50–500 nucleotides per second. DNA polymerase also edits during this process, backing up to correct mismatches, which is followed by further proofreading and mismatch repair by its $3' \rightarrow 5'$ exonuclease site. Although these enzymes vary in structure and efficiency between and even within species (they themselves are products of heritable variation, and hence natural selection), estimates of

4. Interestingly, Florián and Leszczyński (1996, 3010) claim that the methods used by researchers to determine ionized and/or wobble base pairing involve conditions far different than those that actually obtain during DNA replication, moreover that wobble mismatches are more easily located and excised by the repair mechanisms than mismatches involving minor tautomers.

the error rate prior to editing and proofreading is around 10^{-3} to 10^{-4} per base pair, and is reduced to around 10^{-9} to 10^{-11} following editing and proofreading (Drake 1991, 140; Goodman 1999, 640; Chou and Reid 1999, 331), although it should be noted that DNA polymerase and its exonuclease also occasionally introduce base-pair mismatches in their attempts at editing and proofreading. (Glickman 1987, 48)

DNA polymerase is a large and complex molecule, comprising approximately 1,000 amino acids. Even so, every part of it is subject to Brownian motion (as well as the DNA molecule itself, though I shall not focus on it), or more accurately thermal motion (noise, wind). Molecular biologists virtually all agree that this thermal motion has to be responsible, in part, for DNA polymerase infidelity (Tom Martin, pers. comm.; Tom Schneider, pers. comm.), in other words that thermal motion can occasionally be strong enough to cause base-pair mismatches such as wobble configurations and transient misalignment. This is where quantum indeterminism can play a further role. The thermal motion constantly acting on every part of DNA polymerase is caused mainly by the motion of water molecules, since the environment of DNA polymerase is mainly water. Water is composed mainly of groups of H_2O molecules (dimers, trimers, etc.), each group held together by hydrogen bonds. The H_2O molecule and its aqueous relatives are relatively small molecules. Accordingly one would expect their motion to be subject to quantum statistical effects. And they are. Not only must their motion be affected by the quantum statistical nature of their constituent electron orbitals, but recent experimental evidence on water polymers has revealed significant proton tunneling through their constituent hydrogen bonds. Pugliano and Saykally (1992, 1993) provided the first definitive measurements of proton tunneling in the water dimer and trimer. More recently Tuckerman et al. (1997) found pronounced proton tunneling in $H_3O_2^-$, while they found that $H_5O_2^+$ behaves in an essentially classical manner. At any rate, the effect of proton tunneling on thermal motion in an aqueous medium should be obvious. Although proton tunneling does not change the overall charge of the polymer, it does change its relative polarity, and hence its interaction with other molecules. Although no quantitative models currently exist for the action of such quantum induced thermal motion on DNA polymerase fidelity (which is understandable given the complexity of DNA polymerase and its activity, as well as competition from other mutation models), it is certainly a reasonable conclusion (given the apparently complementary role of hydrogen bonds and geometry discussed above) that quantum induced thermal motion on DNA polymerase is often the cause of base-pair mismatches.[5]

5. The role of temperature in evolution has of course much wider implications. Reanney

To all of the above, one might reply by appealing to the facts that (1) DNA has varying rates of mutation, such that some segments of DNA are what are called mutational hotspots, (2) mutations are often induced by chemical agents such as benzene and ionizing radiation such as X-rays, and (3) mutation rates seem to be products of natural selection. Does not all of this reveal that mutation is basically a deterministic rather than random process? I suggest not. Although mutational hot spots are "barely understood" (Goodman 1999, 641), it is known that they are often GC rich (Graur and Li 2000, 37–38) and that the efficiency of their repair depends on the kind of mismatch (Pu:Pu, Py:Py, or Pu:Py) as well as on the flanking base pairs. (Chou and Reid 1999, 331) It is also known that natural selection can drive mutation rates, achieving an equilibrium (or close to it) between fidelity and the physiological cost of improving fidelity (slower replication, additional repair mechanisms, etc.). (Drake 1991, 140–142) Combined with the facts of *induced* mutations, all of this means that there are factors which affect the rates of mutation. But there is no reason to jump to determinism here. All of these affected rates are still statistical, and quite possibly irreducibly statistical. The situation is analogous to radioactive decay. Given an atom of radium, for example, one cannot predict when it will decay into an atom of radon, but nevertheless one can make a statistical prediction (the half life) about a large sample of radium atoms. The same can be said about mutations. Given any base pair in a gene, one cannot possibly predict that it will mutate during a particular round of DNA synthesis, but one can give a probability. The fact that variable factors such as ionizing rays, flanking bases, GC rich genes, and natural selection can either raise or lower that probability need be no different, ontologically, than the fact that different radioactive elements each have a different half life. What the above variable factors do is affect the energy thresholds for quantum jumps, whether Watson-Crick tautomeric shifts or quantum tunneling, as well as the probability of thermal motion affecting DNA fidelity. But just as with radioactive decay, we are still dealing with, to use John Drake's apt phrase (pers. comm.), "constrained randomness."

4. Conclusion. Graves et al. take the view that just as "Macrolevel physical processes and objects asymptotically approach determinism," in spite of quantum indeterminism, so too "biological processes . . . should also as-

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and Pressing (1984), for example, in addition to showing that "the error rate increases monotonically with temperature" (74), discuss the role that temperature must have played in the early evolution of genetic systems, including the synonymy of the genetic code, the evolution of DNA repair mechanisms, and the origin of diploidy in eukaryotes.

ymptotically approach determinism and should thus be describable, as macrolevel physical processes are, with a nonprobabilistic theory." (145) In the previous section, rather than argue for a single robust pathway from quantum indeterminism to evolutionary biology via point mutations, I argued that the current state of molecular biology strongly indicates that there are a number of such pathways, which together make quite unjustified the armchair claim that there are none.[6]

The importance of this topic cannot be overstated. It is important not only for a properly conceived realist theory of evolution, but also (1) for determining the proper role of biologists when making theories, (2) for determining whether biology is in fact autonomous from physics and chemistry, and (3) for its implications for the many attempts to harmonize theology with biological evolution. I shall here comment briefly on each of the latter three.

Graves et al. argue that if the "percolation" argument of Brandon and Carson is basically correct, then the empirical search for causal mechanisms in biology will be in vain. Using the example of plant clones raised in an ostensibly identical environment, they state that "the indeterminist is no biologist" and that the *real* biologist will " 'posit' hidden variables and seek evidence for them in more carefully constructed experiments." (153) This characterization of the true biologist, and the fear which underlies it, is misplaced. The plant biologist can accept that some variation among the clones is due to genuine chance in cell reproduction and yet go on to search for genuine causal differences of the variation ("hidden variables"). He or she might very well find some, identifying causes moreover that (given the relatively low frequency of mutations) can be made into generalizations. Indeed molecular biologists do this all the time! And I can see no reason why other biologists need be any different, since all of their fields involve "noise" to some extent. (Johnson 1987)

At any rate, I suspect (though I cannot prove) that the real debate between Brandon and Carson on the one hand and Graves et al. on the other is about the autonomy of biology from physics and chemistry. It is clear from Horan (1994, 83 n. 1) and Rosenberg (1994, 60–61), which serve as the background for Graves et al., that these authors wish to exclude from biological processes the causes of mutations, whatever they might

6. In this paper I have not explored pathways outside of point mutations. But this should not be taken to imply that there are none. Kohen and Klinman (1999), for example, explore recent experimental findings on enzyme catalysis for which classical explanations are insufficient, and for which hydrogen tunneling must be invoked. Such lines of research only further amplify and strengthen the general philosophical stance of this paper, but for obvious reasons they could not be explored here.

be. But molecular biologists, many of whom have a background training in physics, generally do not think in such terms. Typical is Haynes' (1987, 3) statement that "Quantum mechanics, thermodynamics, and molecular biology collectively reveal that the laws governing the fundamental transformations of matter and life are, at bottom, statistical in character. They are the laws of aggregates and averages, based upon chance events, statistical fluctuations, and molecular accidents." The issue is whether the quantum events that cause mutations are *part* of the processes of biological evolution or are at a lower level and so are *not* part of those processes. The key for molecular biologists is to be found in Haynes' words "at bottom." Of course one can employ semantic games all one wants, and employ academic bias all one wants, but (presuming the truth of modern physics) the fact remains that biological evolution is a *physical* process with quantum indeterministic causes of phenotypic variation, and hence an inherently statistical process. Any characterization of biological evolution, or modern evolutionary theory, that fails to incorporate this fact is misleading at best and obscurantist at worst. The upshot is that if one wants to affirm the autonomy of biology from physics and chemistry, the determinism/indeterminism route is not the way to go.

For most people, of course, academics and nonacademics alike, the real issue is not whether biology is autonomous from the lower level sciences, but rather what the role of quantum chance in evolution means for religion. Naturally this wider issue is not a prime concern of evolutionary biology *per se*, with its methodological materialism. But it does have immense social ramifications, in particular for science education at the primary and secondary school levels, and ultimately for the reception of evolutionary biology by the public as a whole. The issue is that molecular biologists typically draw atheistic conclusions from their science. Monod (1971, 112–113), for example, states that "chance *alone* is at the source of every innovation, of all creation in the biosphere. Pure chance, absolutely free but blind, at the very root of the stupendous edifice of evolution: . . . It is today the *sole* conceivable hypothesis, the only one that squares with observed and tested fact." Similarly Haynes (1987, 1), connecting modern physics and biology to the Epicurean idea of the "indeterminate swerve," likens the universe and its parts not to a machine but to "a game of chance, played out on a vast, microcosmic wheel of fortune." Alan Weiner (pers. comm.) put it most succinctly with "chemistry constrains but chance rules." Such statements raise anew the old topic of the proper boundary of science. But more importantly, granting the fact of evolution, if it is indeed true that at least many of the mutations that feed natural selection are the product of quantum chance, then it does indeed seem quite difficult if not impossible to reconcile this in any rational way with the hope of God-directed evolution. But this is a topic for a later paper (Stamos 2001).

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