Proton Tunneling in DNA and its Biological Implications*

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1. INTRODUCTION

TODAY there seems to be little doubt that many of the fundamental biochemical processes in the living systems are directly connected with the transfer of electrons and protons. Since these are fundamental particles which do not obey the laws of classical physics but the laws of modern quantum chemistry, the electronic and protonic structure of biologically interesting molecules and systems has to be treated by quantum chemistry. This has lead to the opening of a new field which has been called submolecular biology or "quantum biology." The principles of quantum mechanics are of fundamental importance not only in treating the ground state and excited states of the biologically interesting molecules but also in connection with the problems of energy storage and the transfer of energy, momentum, mass, and charge.[1]

In his lecture at this symposium, Professor Bernard Pullman[2] has just pointed out that the flexibility and the extremely high mobility of the living systems in many cases seem to be directly connected with the properties of the "mobile electrons" of the conjugated systems which occur as essential constituents of many of the biologically important molecules. The Pullmans are treating these systems in the so-called Hückel approximation, and it should perhaps be emphasized that this highly semi-empirical approach, which is usually considered as a rough and highly approximate form of the Hartree–Fock scheme, may have a still deeper background in terms of the exact SCF theory discussed at another session of this conference.

We will now turn our interest from the electrons to the protons, and particularly to the protons which occur in the hydrogen bonds between the base pairs in the Watson–Crick model of DNA (deoxyribonucleic acid), i.e., the giant molecule which is believed to be the essential hereditary substance carrying the genetic information in the cell. According to this model, the genetic code is essentially contained in the arrangements of the hydrogen bonds, and the purpose of this note is to study these bonds quantum mechanically and show that, after a DNA replication, the protons are necessarily in nonstationary states which implies that there is a certain probability for "quantum jumps" which will lead to discontinuous changes of the code which will show up and get manifested at the next DNA replication. This mechanism may be responsible for the occurrence of spontaneous mutations, the phenomenon of aging considered as a loss of useful genetic information, and the spontaneous occurrence of tumors (and cancer) as a consequence of somatic mutations depending on the accumulated effects of code changes in a certain direction.

2. WATSON-CRICK MODEL OF DNA

Let us first consider the experimental evidence that the genetic information in the living organisms is essentially carried by giant molecules.

Through his work in immunology, Griffith could in 1928 show that the hereditary properties of pneumococci could be transformed by a chemical compound which seemed to carry the genetic message. In 1944, Avery[3] and his co-workers could conclusively identify this substance as deoxyribonucleic acid (DNA—one of the nucleic acids well known from the last century.[4]

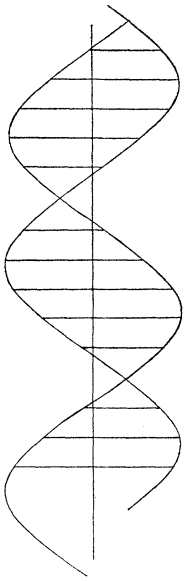
* Work supported in part by "King Gustaf VI Adolf's 70-Years Fund for Swedish Culture" and by the Wallenberg Foundation, and in part by the "National Cancer Institute of the U. S. Public Health Service." Contract CA 06850–01.

[1] The need for the development of a submolecular biology has been particularly strongly emphasized by A. Szent-Györgyi, *Introduction to Submolecular Biology* (Academic Press Inc., New York, 1960); see also M. Kasha and B. Pullman, *Horizons in Biochemistry,* Albert Szent-Györgyi Dedicatory Volume (Academic Press Inc., New York, 1962); R. B. Setlow and E. C. Pollard, *Molecular Biophysics* (Addison-Wesley Publishing Company, Inc., Reading, Massachusetts, 1962).

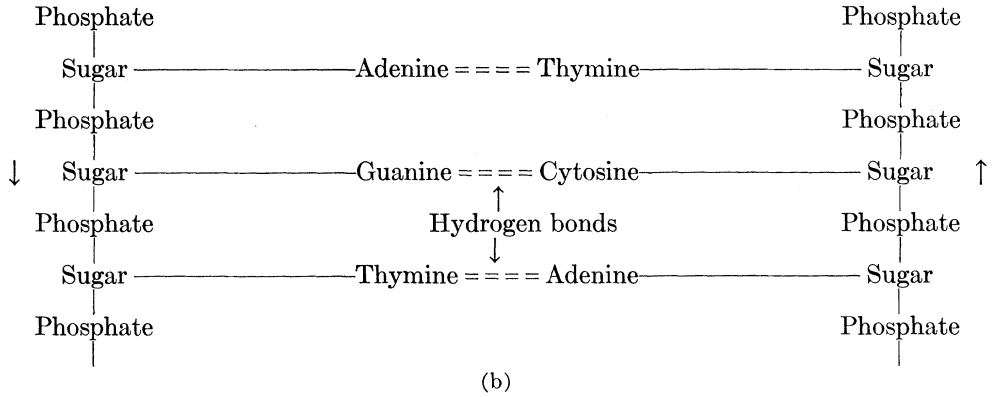
[2] This lecture which was also presented at the Rättvik Symposium arranged in connection with the Summer Institute on Quantum Chemistry and Solid-State Physics in Uppsala, Sweden, August, 1962, has been published in B. Pullman and A. Pullman, Nature **196**, 1137 (1962).

[3] O. T. Avery, C. M. MacLeod, and M. McCarty, J. Exptl. Med. **79**, 137 (1944).

[4] The nucleic acids were discovered by F. Miescher in 1868; for a comprehensive survey of their properties, see J. N. Davidson, *The Biochemistry of the Nucleic Acids* (Methuen and Company Ltd., London, 1960), 4th ed.



(a)



(b)

FIG. 1. (a) The double helix of DNA in the Watson–Crick model. The diameter is approximately 20Å; the length may be several thousand angstroms. (b) Linear representation of the DNA molecule

One knew that these molecules were polynucleotides formed by four nucleotides derived from the nucleotide bases adenine (A), thymine (T), guanine (G), and cytosine (C) by adding pentose sugar and phosphate groups. Through chromatographic work, Chargaff[5] could show in 1950 that, in DNA, the molar contents of the two bases adenine and thymine were always equal and that the same is true for the two bases guanine and cytosine.

Using Wilkins's[6] x-ray data for DNA, Watson and Crick[7] suggested in 1953 a stereo model in which DNA consists of a double helix, where the strands are sugar-phosphate chains joined by pairs of nucleotide bases held together by hydrogen bonds. The pairing of the bases is further specific in the combinations A–T, G–C, in agreement with Chargaff's data, and each base has hence a specific "complementary" base (see Figs. 1 and 2). The deeper reason for the complementarity comes from the limited possibilities for the formation of hydrogen bonds between the bases involved. A hydrogen bond is here essentially a proton H shared between two electron pairs : situated on oxygen or nitrogen atoms. The model implies that, if one strand has a specific base sequence, say ATGACTG···, the other strand has the complementary sequence TACTGAC···, and it is believed that one of these four-letter sequences essentially contains the genetic code.

Before the cell division, the DNA molecule should in some way be duplicated and, according to Watson and Crick, the double helix starts unwinding at the same time as each strand starts building its own complement out of the nucleotide material in the environment. In this way, one obtains two identical DNA

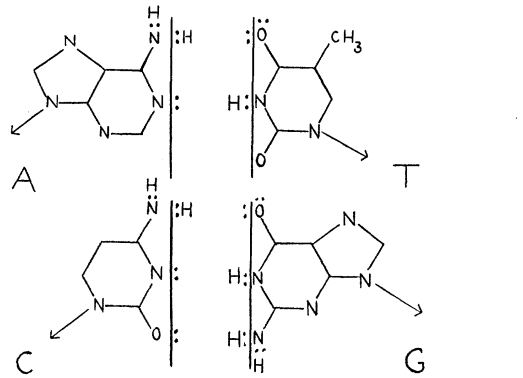


FIG. 2. The nucleotide bases occurring in DNA. The arrows indicate the bonds towards the sugar groups in the strands; the upper parts of the molecules form the bottom of the "deep groove" of the double helix.

[5] E. Chargaff, F. Magasanik, E. Vischer, C. Green, R. Doniger, and D. Elson, J. Biol. Chem. **186**, 51 (1950); E. Chargaff, Experientia **6**, 201 (1950); see also E. Chargaff, *The Nucleic Acids*, edited by E. Chargaff and J. N. Davidson (Academic Press Inc., New York, 1955), Vol. I, p. 307.

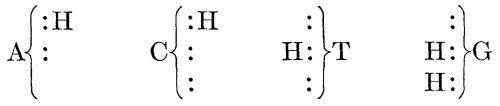
[6] M. H. F. Wilkins, A. R. Stokes, and H. R. Wilson, Nature **171**, 738 (1953); M. H. F. Wilkins, W. E. Seeds, A. R. Stokes, and H. R. Wilson, Nature **172**, 759 (1953). See also M. H. F. Wilkins, in *Biological Structure and Function, Proceedings of The First IUB–IUBS Joint Symposium, Stockholm, 1960*, edited by T. W. Goodwin and O. Lindberg (Academic Press Inc., New York, 1961), p. 13.

[7] J. D. Watson and F. H. C. Crick, Nature **171**, 737, 964 (1953); F. H. C. Crick and J. D. Watson, Proc. Roy. Soc. (London) **A233**, 80 (1954).

molecules each containing the original genetic information.

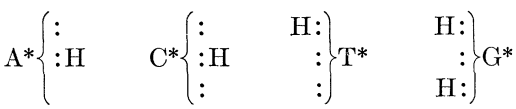
The replication process is complicated by the fact that the total energy, angular momentum, and momentum has to be conserved, and many types have been discussed in the literature.[8,9] The actual details will not influence the phenomena we are going to discuss in the following in a first approximation.

In order to study the concept of complementarity in greater detail, it is worthwhile to consider the parts of the bases which take part in the formation of the hydrogen bonds (see also Fig. 2). Writing the bases in this particular way, we can introduce the following short-hand for the "proton–electron pair" code:



The bases A and C have *equivalent codes* (with respect to the upper two positions) and the same is true for T and G. In these figures, we have emphasized the electron lone pairs : and the protons H, and we note that a hydrogen bond is essentially a proton shared between two electron lone pairs associated with different atoms.

In addition to the normal forms, we will now also consider the tautomeric forms obtained by moving a proton from the upper lone pair to the middle one, or vice versa. Denoting the "imine" forms of A and C by A* and C*, respectively, and the "enol" forms of T and G by T* and G*, respectively, we obtain the following "proton–electronpair" codes:



From a study of the hydrogen bonds, it is now clear that A* will no longer combine with T but with C, etc., so that one obtains the combinations

$$\text{A*–C}\,,\quad \text{A–C*}\,,\quad \text{G*–T}\,,\quad \text{G–T*}\,.$$

This means that the complementarity between the bases is completely changed, and the movement of a single proton within a base will in this way influence the genetic message and introduce an error at the first cell duplication, according to the following scheme:

original sequence:	A G T C A T T G C A
tautomeric change:	A G T* C A T T G C A
complementary sequence:	T C G G T A A C G T
new sequence:	A G C C A T T G C A

The general diagram below gives a comparison between the normal and the tautomeric replication of the single bases with the complementary base in the middle:

Normal	Tautomeric
A–T–A	A*–C–G
T–A–T	T*–G–C
G–C–G	G*–T–A
C–G–C	C*–A–T

The genetic error undergoes "biological amplification" by the factors 2, 4, 8, 16 $\cdots$ and may hence soon become recognizable.

Watson and Crick[10] have suggested such a mechanism to explain the *mutations:* "Spontaneous mutations may be due to a base occasionally occurring in one of its less likely tautomeric forms." We note that this is in complete accordance with the general idea expressed by Delbrück and discussed by Schrödinger.[11] These authors emphasized that there ought to be a close parallelism between the immense stability of the hereditary substance over thousands of years and the stationary state of a giant molecule or "aperiodic solid," and that further the discontinuous changes of the genetic code leading to mutations should correspond to "quantum jumps" between various stationary states. It seems now as if these quantum jumps would be associated with proton transfer within the nucleotide bases in the DNA molecule.

These ideas about the origin of the mutations have been tested experimentally. A chemical like nitrous acid will cause an oxidative deanimation of the bases which changes the proton–electronpair code, and mutations will then result.[10] These mutations are induced. Here we essentially discuss the nature of the spontaneous mutations which are not caused by any outer influence on the DNA molecule.

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[8] For a survey of processes suggested, see M. Delbrück and G. S. Stent, *The Chemical Basis of Heredity* (Johns Hopkins Press, Baltimore, Maryland, 1957), p. 699.

[9] For a mechanism which preserves not only the total energy but also the total angular momentum and momentum, see P.-O. Löwdin, Technical Note 85, Uppsala Quantum Chemistry Group, November, 1962 (unpublished).

[10] See e.g. "Mutation," Brookhaven Symp. Biol. No. 8, 1956 (U. S. Department of Commerce, Washington, D. C., 1956).

[11] E. Schrödinger, *What is Life? The Physical Aspects of the Living Cell* (Cambridge University Press, New York, 1945). It should be noted that Schrödinger presented his ideas about the "aperiodic solid" in his Dublin lectures 1942, i.e., two years before Avery's discovery of the role of the nucleic acids in heredity.

3. NATURE OF THE HYDROGEN BOND

Since the Watson–Crick model essentially utilizes the hydrogen bond in the definition of the complementarity between the nucleotide bases, it may be worthwhile to study the properties of this bond in greater detail.

Chemical experience has shown that a hydrogen atom attached to an electronegative atom in a molecule may also be attracted to another electronegative atom in a different molecule, in this way leading to a "hydrogen bond" between the two molecules. Sometimes there is also an internal hydrogen bond between two electronegative atoms within the same molecule. The atoms which form the strongest hydrogen bonds are in order after decreasing strength: fluorine, oxygen, and nitrogen, whereas weak bonds are formed by chlorine and carbon. Experimentally the properties of the hydrogen bonds have been studied extensively and, for a survey, we would like to refer to Pimentel and McClellan[12] and to the proceedings[13] from the 1957 conference.

Electron–proton formulation of the hydrogen bonding. In order to investigate the properties of the hydrogen bond, one has to understand the electronic structure of the atoms involved. A carbon atom in a conjugated system, say a benzene ring, has three sp^2 hybrides in the molecular plane forming 120° angles with each other and a $2p_z$ orbital perpendicular to the plane offering an orbital to the π–electron system. In each CH bond, there is an electron pair, and if one drops the proton into the carbon nucleus, one obtains a nitrogen nucleus with an electron lonepair in a sp^2 hybrid pointing out in space. This lonepair will attract every proton (or positive group) in the neighborhood, and this explains the tendency of pyridine to try to catch a proton and become a pyridinium ion $C_5NH_6^+$, i. e. its "base" character (see Fig. 3).

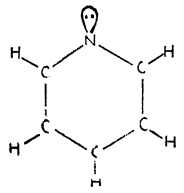


FIG. 3. Nitrogen atom in pyridine ring with an electron lone-pair in a sp^2 hybrid pointing out from the ring.

If there are several molecules having such electron lonepairs in a system, there may be a competition to catch the protons in the environment which leads to the formation of the above-mentioned hydrogen bonds. In this type of formulation, a hydrogen bond is characterized as a *proton shared between two electron lonepairs* (see Fig. 4).

In a hydrogen bond, the attraction of each electron

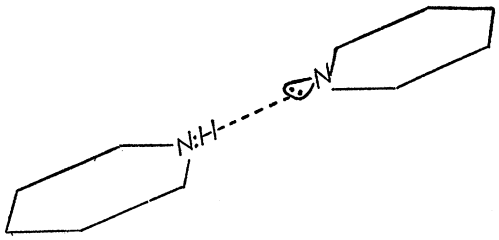


FIG. 4. Hydrogen bond between two pyridines formed by two-electron lone-pairs competing to get the same proton.

lonepair on a proton is represented by a deep single-well potential. Since the superposition of two such potentials is usually a double-well potential with a "bump" in the middle, the proton has classically two equilibrium positions—one close to each one of the two electron lonepairs involved:

$$\mathrm{N:H---:N} \qquad \mathrm{N:---H:N}.$$

If these equilibrium positions are equivalent, one can expect that, under certain conditions, the proton may jump from one position to another. Since such a jump will influence the gross electric neutrality of the entire environment, it may induce other proton jumps so that the final effect will be a collective phenomenon. This process in the ice crystal has been studied by Pauling,[14] and he shows that it has important consequences for the residual entropy of ice. In classical physics, such "proton jumping" will take place only if the necessary activation energy is available.

In quantum mechanics, the situation is somewhat different, since the proton is a "wave packet" which may penetrate even into such regions as were forbidden for a classical particle. Already the first study of the harmonic oscillator in modern theory showed that the wave function could be essentially different from zero even outside the classical "turning points" (see Fig. 5). This leads to the famous quantum-mechanical *"tunnel effect"* which depends on the fact that the quantities kinetic energy and potential energy are not simultaneously measurable. The phenomenon implies that, if the potential energy curve shows two classically permitted intervals separated by a forbidden region, a quantum-mechanical par-

[12] G. C. Pimentel and A. L. McClellan, *The Hydrogen Bond* (W. H. Freeman and Company, San Francisco, 1960).

[13] *Hydrogen Bonding,* Papers Presented at the Symposium on Hydrogen Bonding, Ljubljana, Yugoslavia, 1957, edited by D. Hadzi (Pergamon Press, London, 1959).

[14] L. Pauling, *Nature of the Chemical Bond* (Cornell University Press, Ithaca, New York, 1939); 3rd ed., p. 464.

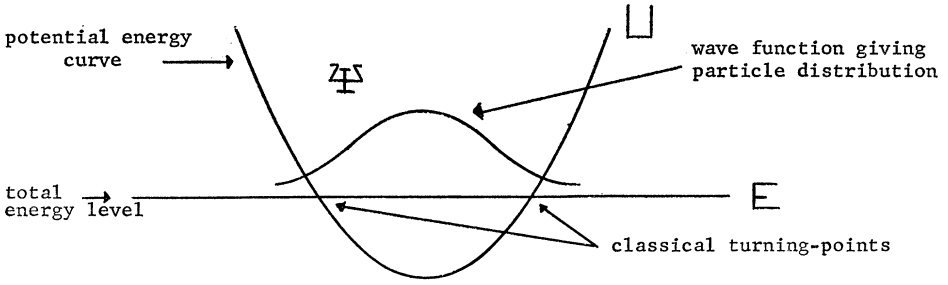


FIG. 5. Ground-state wave function of harmonic oscillator.

ticle may leak through the potential barrier from one "permitted" state to another.

The effect was first used by Gamow to explain the general phenomenon of radioactivity, which implies a transition from a bound state to a state in the continuum with a free particle emitted. The fact that the radioactive half-life times range from small fractions of seconds to thousands of years shows that tunneling probabilities can take values of all orders of magnitude. In molecular spectroscopy, the tunnel effect is quite well known as causing the phenomenon of predissociation. Another example is given by the "ammonium-clock." In solid-state physics, the effect has been utilized for the technical construction of certain types of semiconductors known as tunneling diodes. There seems also to be good reasons for believing that corrosion may be due to loss of order through particle-tunneling.

In ordinary chemistry, the tunnel effect has so far been of smaller importance. In the theory of chemical kinetics, one would usually consider only processes which would have sufficient energy to take the components above the potential barrier between the two states involved, and the effect of tunneling is usually so small that it can be neglected. However, in certain biochemical processes where one has the effect of "biological amplification," it could very well happen that even the chemical effects of tunneling may show up, as we shall see below.

Let us now return to the hydrogen bond and the double-well potential. The behavior of the proton is regulated by the time-dependent Schrödinger equation

$$\mathcal{H}_{op}\Psi = -\frac{h}{2\pi i}\frac{\partial\Psi}{\partial t},$$

and a solution in terms of an expansion in terms of stationary states is easily obtained. The eigenvalue problem $\mathcal{H}_{op}\Psi = E\Psi$ is conveniently treated by the WKB method[15] and its refinements, and the single-proton problem does not offer any major difficulties in principle.

If the double-well potential is symmetric, the quantum-mechanical wave functions for the stationary states are necessarily "gerade" or "ungerade" which corresponds to a 50–50 distribution of the proton over both positions. On the other hand, if the proton is initially localized in one of the potential wells, the system is in a nonstationary state, and the proton will oscillate between the two classical equilibrium positions with a frequency determined by the energy difference between the "ungerade" and the "gerade" state divided by Planck's constant h. For an asymmetric potential, the components of the

[15] See e.g. N. F. Mott and I. N. Sneddon, *Wave Mechanics and its Applications* (Clarendon Press, Oxford, England, 1948), p. 15; L. D. Landau and E. M. Lifshitz, *Quantum Mechanics* (Pergamon Press, London, 1958), p. 171.

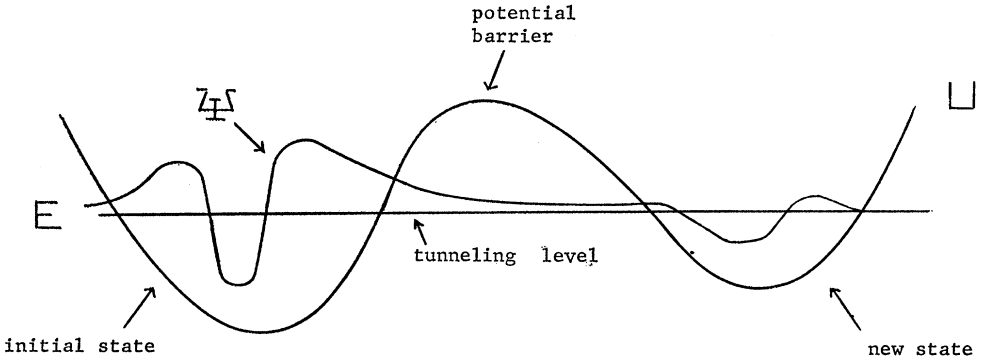


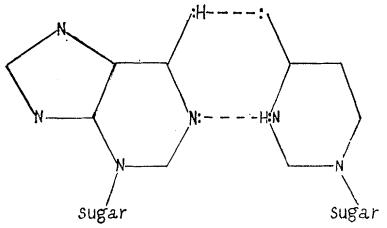
FIG. 6. Quantum-mechanical tunnel effect permitting a wave packet to penetrate from one potential well to another.

original proton wave packet associated with the lower-lying energy levels of the deeper well will remain comparatively stationary, whereas the components associated with energy levels above the bottom of the other well will penetrate the barrier more easily and start oscillating. The analysis of the original proton wave packet involves an interesting phase problem, and, since the energy distribution is temperature dependent, the whole phenomenon is also temperature dependent.

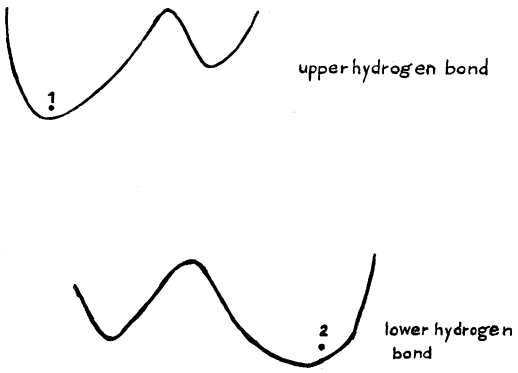
Today the existence of the double-well potential has been well established[16] and, for many compounds involving nitrogens, the tunneling frequencies have been found to be of the order 10^{11} sec^{-1}. The theoretical literature is rich, and the results seem to be in good agreement with experience.[17,18]

4. PROTON TUNNELING IN DNA AND ITS BIOLOGICAL IMPLICATIONS

The hydrogen bonds play a fundamental role in the complementarity concept developed by Watson and Crick in their stereo model of DNA. One can condense the essential features of the base pairing described in Fig. 7 in the schematic diagram:



There are at least two hydrogen bonds involved, and the problem of the genetic code is hence concerned with the question of the *motion and stability of two protons in a four-well potential:*



i. e., one has to treat a quantum-mechanical two-body problem. Since the movements of the protons will further polarize the electron clouds and hence also change the potentials, a complete solution will undoubtedly be rather complicated. For the sake of simplicity, we will consider the two double-well potentials as fixed.

Since it is essential for the entire Watson–Crick model that the protons remain in their "normal" positions in the base pairs in order to represent a pure genetic message, one has to assume that the double-well potentials are *highly asymmetric.* A fundamental quantum-mechanical problem in the study of DNA is hence to investigate whether this is actually the case. In a highly asymmetric potential, a large part of the wave packet may remain in the deeper well, whereas only a smaller part of the packet will actually oscillate between the two positions. The frequencies involved may be obtained from the Schrödinger equation.

The tunneling times will depend essentially on the height and the form of the barrier. In DNA, the form of the double-well potentials regulating the hydrogen bonds depend not only on the base pair involved but also on neighboring pairs, their net charges, and the entire electric environment. The tunneling time is hence not only characteristic for a certain biological specimen but is also a function of the position in the DNA molecule involved. The tunneling time is very likely also temperature dependent, even if the protons are well shielded in the double helix. The main problem is whether the tunneling time is very short in comparison to the replication time, or whether there exist organisms where the penetration of the barrier is slow in comparison to the replication. This is still to be investigated.

It should always be remembered that, in Born's interpretation of quantum mechanics, the quantity $|\Psi|^2$ represents the probability density for finding the proton in a specific position. The tunneling of the wave packet is hence a time-dependent process which

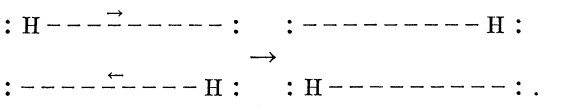
[16] C. L. Bell and G. M. Barrow, J. Chem. Phys. **31**, 300 (1959); C. Haas and D. F. Hornig, J. Chem. Phys. **32**, 1763 (1959); H. Zimmermann, Z. Elektrochem. **63**, 601 (1959); **65**, 821 (1961); N. Joop and H. Zimmermann, Z. Elektrochem. **66**, 440, 541 (1962).

[17] C. A. Coulson, in *Hydrogen Bonding*, Papers Presented at the Symposium on Hydrogen Bonding, Ljubljana, Yugoslavia, 1957, edited by D. Hadzi (Pergamon Press, London, 1959), p. 339; E. R. Lippincott, J. N. Finch, and R. Schroeder, *ibid.*, p. 361; L. Hofacker, *ibid*, p. 375; N. D. Sokolov, *ibid.*, p. 385; M. Davies, *ibid.*, p. 393; and several other contributions. See also the survey in L. E. Orgel, Revs. Mod. Phys. **31**, 100 (1959).

[18] L. Hofacker, Z. Naturforsch. **13a**, 1044 (1958); I. Fischer-Hjalmars and R. Grahn, Acta Chem. Scand. **12**, 584 (1958); R. Grahn, Arkiv Fysik **15**, 257 (1959); **19**, 147 (1961); **21**, 1 (1962); **21**, 13 (1962); **21**, 81 (1962).

is going to influence the properties of the genetic code. In the discussion, it is convenient to distinguish between two cases which approximately correspond to the spontaneous and induced phenomena:

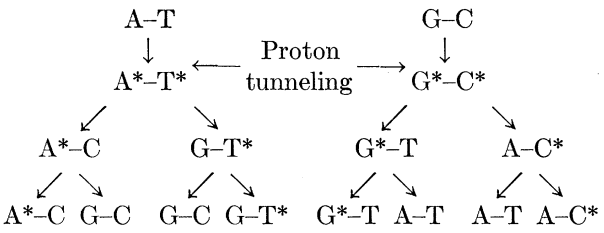
(*a*) *Bases with equal charge.* In this case the tunneling of one proton in one direction will very likely induce a tunneling of the other proton in the reverse direction to keep balance between the gross electric charges, so that



This simultaneous proton tunneling implies the base transitions

$$\text{A–T} \rightarrow \text{A*–T*}\,, \qquad \text{G–C} \rightarrow \text{G*–C*}\,,$$

which leads to the production of *pairs* of tautomeric bases. If the hydrogen bonds get released in this position, the tautomeric forms will lead to errors in the next replication, i. e., to mutations according to the following scheme:



Hence the proton tunneling leads to the following change of base pairs:

$$\text{A–T} \longrightarrow \text{G–C}$$
$$\text{G–C} \longrightarrow \text{A–T}\,,$$

where a base goes over into another base of the same type, i. e., a purine into a purine and a pyrimidine into a pyrimidine. Mutations of this type have been called "transitions" and are characterized by the fact that they are reversible, i. e., a mutant may go back to the wildlife type.

In this connection, it should be observed that the tunneling probabilities depend not only on the base pair involved but also on the electrostatic environment, the neighboring base pairs, etc., which may explain the occurrence of "hot spots."

At a DNA replication, the protons have to "choose sides," and the proton code immediately after a DNA replication represents actually a *nonstationary state* from the quantum-mechanical point of view. The time evolution of the system and particularly the penetration of the potential barrier in the double-well potential represents a loss of the genetic code which should perhaps be considered as the primary cause of *aging*. The aging is thus a process which goes on continuously in the DNA molecule but gets "manifested" at the replications.

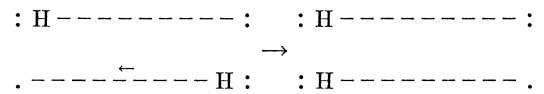
Proton tunneling may finally be of importance in connection with the occurrence of spontaneous tumors. The growth of an individual is a highly refined balance between factors which enhance the cell duplication and other factors which limit this duplication so that the organism takes a specific shape. The entire process is stimulated and controlled by various enzymes, and there is a feedback from the environment about which we know, at present, very little. If there is a *somatic mutation*, i. e., a change of the genetic code in a DNA molecule in the body of an organism, the change may influence the protein synthesis and the balance between the enhancing and controlling enzyme actions in the growth cycle. Actually, the new genetic code may lead to the development of a "new individual" within the individual, i. e., a tumor.

Since the spontaneous somatic mutations apparently depend on the same quantum-mechanical "tunnel effect" as the aging process, there ought to be a clear correlation between age and the occurrence of spontaneous tumors. This gives an explanation of the experimental fact that there seems to be an increasing probability for the occurrence of spontaneous tumors with increasing age. If aging may be described as the result of the accumulation of proton errors, the occurrence of tumors may depend on the fact that the accumulation has passed a certain limit in a particular direction.

It is evident that not all types of tumors have to be malignant. However, if the balance between the enzymes enhancing the DNA replication and the cell duplication and the enzymes checking this process are disturbed in favor of the former, there may develop a malignant tumor. Cancer will here be described as the growth of such abnormal cells in the living organism as have a higher rate of metabolism than the normal cells and which hence may take over the normal material in large areas of the organism and form malignant tumors. In the *deletion hypothesis*, cancer is essentially assumed to be caused by the fact that the growth-controlling enzymes are deleted. This means that, if through proton tunneling, the DNA molecule loses its ability to regulate the synthesis of these specific enzymes, spontaneous cancer will develop. The occurrence of spontaneous cancer would, in this model, depend on a quantum-mechanical tunnel effect of a statistical nature involving the movement of two protons over a distance

of about 1 Å = 10^{-8} cm. One could then understand why cancer can occur at young age, but also why the probability goes up highly with increasing age.

(*b*) *Bases with unequal charge.* If one of the bases in a pair has obtained an extra charge, the shape of the double-well potential is changed and the probability for a proton tunneling is often greatly increased. Under these conditions, the proton transfer goes essentially in one direction:



This leads to transitions of the type A–T → A^+–T^- or A^-–T^+ and the type G–C → G^+–C^- or G^-–C^+. In this case one obtains two ionic tautomeric forms which otherwise do not appear in the Watson–Crick model and which can be expected to cause mutations of a somewhat different type.

Since now the fundamental proton–electronpair code is lost, there will be difficulties in the replication scheme. There is actually no normal nucleotide which could combine with A^+ and T^+, and the occurrence of these ions may hence cause *deletions* in one strand of the base sequence, whereas the ions A^- and T^- lack code specificity and may combine with all four normal bases. Since a deletion always means loss of genetic information, the corresponding mutation would be irreversible.

One may wonder under what conditions the bases within a pair get unequal charges. Through electronic donor–acceptor reactions with other molecules, an electron may be added (or removed) to the π-electron cloud of one of the bases. One electron is further often removed from the π part of one of the bases through the (direct or indirect) effect of ionizing radiation. An important process is probably the addition of a proton to one of the purine bases through bonding to one of the extra electron lonepairs available at the N_3 and N_7 positions, which means that proper attention should be given also proton reactions. It should finally be mentioned that the double-well potential may be disturbed through additional electrostatic potentials from outer sources, dipole double layers, etc. The dimensions may also be changed through external pressure, ultra-sound waves, etc. Other interesting problems to be studied include the effect of radiation in resonance with the proton tunneling frequency, as well as the effect of strong magnetic fields on the proton spins. It is evident that many of these phenomena are closely connected with the problems of induced mutations and carcinogenesis.

5. DISCUSSION

The problem is now how the genetic information contained in the DNA molecule determines the biological properties of the species and individual under consideration. Each species is characterized by its proteins, and of particular importance are the enzymes which catalyze the entire metabolism. The proteins are essentially linear structures built up from 20 amino acids, and the biochemical properties are determined by the sequence of the amino acids. This sequence must, of course, ultimately be determined by the base sequence in DNA, and the question of the connection between these two linear arrangements gives rise to the coding problem.

Studies of the cytoplasm have revealed that the protein synthesis takes place in small bodies called ribosomes, and that it is regulated by RNA (ribonucleic acid). However, it has turned out that RNA is not a single type of molecule but a complex of molecules with various biochemical functionings.[19] The actual genetic information seems to be contained in an enormously long, linear, single-stranded molecule called messenger–RNA which has originally in some way picked up the information at the DNA in the cell nucleus. The dimensions are such that the ribosome is a comparatively small particle in the form of a "ball" or ring gliding along the giant RNA chain.

For the linear arrangement of the amino acids in the protein, Crick and Hoagland[19] have introduced the so-called adapter hypothesis according to which the amino acids are picked up by small pieces of RNA molecules called "soluble RNA" or sRNA. "The position of a particular amino acid is then determined not by the amino acid itself but by the hydrogen bonding between the messenger-RNA template and a complementary nucleotide sequence in the sRNA carrying the amino acid." Experimental evidence seems to verify this idea and the role of both messenger-RNA[20] and sRNA.[21]

Experimental evidence indicates that the base ratios of messenger-RNA are closely analogous to those found in the corresponding DNA, and it seems hence natural to assume that DNA in some way acts as a template. It has been observed[22] that the deep

[19] See e.g. F. H. C. Crick, Symp. Soc. Exptl. Biol. **12**, 138 (1958); M. B. Hoagland, "Structure and Function of Genetic Elements," Brookhaven Symp. Biol. No. 12, 40 (1959); J. Brachet, Nature **186**, 194 (1960).

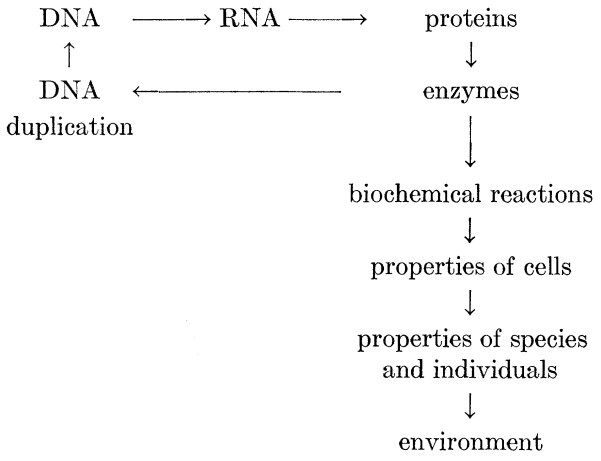
[20] H. Fraenkel-Conrat, A. Tsugita, M. Nirenberg, and J. H. Matthaei, Proc. Natl. Acad. Sci. U. S. **48**, 846 (1962).

[21] F. Chapeville, F. Lippman, G. Ehrenstein, B. Weisblum, W. J. Ray, Jr., and S. Benzer, Proc. Natl. Acad. Sci. U. S. **48**, 1086 (1962).

[22] G. Stent, Adv. Virus Research **5**, 95 (1958); G. Zubay, Nature **182**, 1290 (1958); Proc. Natl. Acad. Sci. U. S. **48**, 456 (1962); G. Zubay, Nature **182**, 112 (1958).

groove of DNA contains an extra "copy" of the proton–electronpair code (see Fig. 2) which may serve as a template for a third helix leading to the formation of messenger-RNA. For a more detailed discussion of this problem, we will refer to another paper.[23]

It seems hence clear that RNA serves as an intermediate between DNA and the proteins, so that DNA regulates RNA which in turn controls the protein synthesis. Since even the enzymes which catalyze the DNA duplication are produced in this way, one obtains the following diagram:



which may be characterized as the "growth cycle." Actually, there is a "feedback" mechanism at several of the other links in the diagram.

6. SUMMARY

Let us now summarize the main points discussed in this paper. Deoxyribonucleic acid (DNA) is considered as the hereditary substance and, according to Watson–Crick's model, the genetic message is contained in a proton–electronpair code which is situated well hidden and shielded in the middle of a double helix. The code consists actually of two complementary pieces of "lock and key" type which together have a great deal of stability. The genetic information is transferred to the cell by means of the formation of messenger-RNA but, during the transcription procedure, the code is not opened up at all, and the message is instead read in an extra "copy" which nature has provided in the deep groove of the double helix. In the replication process, the code is opened only momentarily to find the correct partners for the doubling of the genetic message. All these precautions give the genetic code an unusual stability and explain its ability to preserve a genetic message intact over thousands of years.

In this paper we have pointed out that, since the protons are not classical particles but "wave packets" obeying the laws of modern quantum theory, the genetic code cannot—in spite of all precautions—be 100% stable. Due to the quantum-mechanical "tunnel effect," there is always a small but finite probability that the protons will change place, alter the genetic code, and give rise to mutations. This implies also that this transfer of protons over a distance of about 10^{-8} cm may be one of the driving forces in the evolution of living organisms on the earth. Since the replication procedure forces the protons to "choose sides" and gives a new DNA molecule with the genetic code in a nonstationary state, there will always be a time-dependent process leading to a loss of genetic information through proton leakage which manifests itself at the next replication. The cell loses thus the ability to synthesize all the enzymes necessary for the metabolism and it seems hence likely that the time-dependent proton tunneling may be the primary cause of the phenomenon of aging. Since the proton tunneling further leads to somatic mutations, the phenomenon may also be responsible for the occurrence of spontaneous tumors and cancer.

It is evident that a model of these biological phenomena where all the emphasis is put on the DNA molecule must be somewhat oversimplified, since there are certainly also other cell constituents which play an important role in these connections. We believe, however, that the picture serves a meaningful purpose as a first approximation.

[23] P.-O. Löwdin, Technical Note 85, Uppsala Quantum Chemistry Group, 1962 (unpublished).

Discussion on the Proton-Tunneling Hypothesis for Dielectric Relaxation in Ice

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This may be of interest in relation to the suggestion of P. O. Löwdin [Proceedings of the Stanford Symposium on Quantum Aspects of Polypeptides and Polynucleotides, March 25–29, 1963 (unpublished)] that a proton-tunneling process may be critically involved in genetic mechanisms.