A Possible Correlation between the Effects of Some Carcinogenic Agents and the Electronic Structure of DNA

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Abstract

The values of the quantum mechanical overlap integrals between the π-orbitals of the superimposed nucleotide bases of DNA show that there is a non-negligible interaction between these bases. The energy levels of the MO's of the adenine-thymine and guanine-cytosine base pairs, known from the literature, differ from each other only by an amount ~0.09 e, which is the width of the second filled energy band of the protein molecule, whereas the overlap integral between the adjacent nucleotide bases is considerably larger than between the parallel polypeptide chains of protein. Therefore, it might be expected that in the DNA macromolecule the energies of the delocalized π-electrons form energy bands.

On the basis of the MO energies of the nucleotide base pairs one can show qualitatively that the energy bands of the DNA molecule are situated in such a manner that the hypotheses for the cancerous effect of radiation and of carcinogenic hydrocarbons, based on the quantum mechanical investigation of the electronic structure of protein, can also be applied to the electronic structure of the DNA molecule. It is understandable that excitation or ionization of the molecule causes the polarization of the double helix forming the DNA, if the molecule within the cell is affected by an electric field parallel to its axis.

We show in the paper that the repulsion energy between the two helices of DNA, caused by the appearance of an electric net charge of e₀ at any end of the macromolecule, may induce with great probability the unwinding of the double helix. Further, we discuss two possibilities for the connection between the unwinding of the DNA particles and the beginning of tumor development.

To support our hypothesis we continue, on the one hand, our quantum mechanical computations concerning the electronic structure of the DNA; on the other hand, preparations are under way for experimental investigations on cultures of cancerous tissues placed in strong electrostatic fields.

As is well known, radiation-induced cancer occurs when the energy hν of the radiation is higher than the threshold value of 3.4 ev (7). Twenty years ago an attempt was made by Schmidt (33-37) to interpret this fact by assuming that at least as much energy was needed for any internal arrangement of the atoms in a gene or in some other important constituent of the cell, which eventually would lead to carcinogenesis. Recently, Mason (22, 23) assumed that, by the effect of radiation with corresponding energy whereby an electron in the protein jumps from the highest filled energy band to the lowest empty band, the macromolecule thus becomes a conductor, and the mechanism of carcinogenesis is somehow induced by this process. Evans and Gergely demonstrated (12) 11 years ago that, if in the molecule of the protein a π-electron interaction is assumed between the individual parallel polypeptide chains connected by H-bonds, the energy levels of the infinitely long π-electron molecular orbitals obtainable in

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this way will form three energy bands. In Table 1 the positions of the individual energy bands are presented for the trigonal stereo structure of the N atom of the peptide group.

Table 1 shows clearly that the macromolecule is not conducting in its ground state. It becomes a conductor, however, if it is excited. The width of the forbidden band is \( \sim 3 \text{ ev} \), and even if this value does not agree exactly with the above-mentioned value of 3.4 ev, the discrepancy is not large. An objection may be raised against the computation that it has been made from a model where the delocalization of the \( \pi \)-electrons has been assumed a priori.\(^1\) However, investigating the semiconductivity of the proteins, Eley and his co-workers (5, 10, 11) found the experimental results to be in good agreement with the theoretical values mentioned above. Thus, the correctness of the model, serving as a starting point for the Evans-Gergely computation, has been supported to a high degree.

Among the compounds with carcinogenic activity, the electronic structure of the angularly condensed hydrocarbons has been carefully investigated. It was stated by A. and B. Pullman (26) that those angularly condensed hydrocarbons exert a carcinogenic effect for which a smaller activation energy than 3.81 \( \text{eV} \) was needed for localization of a \( \pi \)-electron pair in the K-region, while at the same time more than 5.66 \( \text{eV} \) of activation energy is necessary to localize the two \( \pi \)-electrons into the more reactive L-region. They assumed that in the transition complex formed by the carcinogenic hydrocarbon and some cell components one of the \( \pi \)-electron pairs of the carcinogenic compound is localized in the K-region; subsequently this double bond splits, and the hydrocarbon binds to the cell component through addition. At the same time, it was also assumed to be very probable that the two bonds between the cell component and the hydrocarbon had partially a double-bond character.

One may note that the carcinogenic hydrocarbons, except for a few exceptional examples, fulfill both above-mentioned conveniently chosen conditions, which cannot be realized in the case of the nonactive compounds. These conditions do not exclude, however, the possibility of the existence of some angularly condensed hydrocarbons, to the K-regions of which some cell components may be bound without showing any carcinogenic activity. Thus, the capacity for addition in the K-region appears to be a necessary, but not always sufficient, condition for carcinogenic activity (6).

A further step to solve the problem was made by Mason (22, 23). He obtained good agreement with the experimental facts, assuming that those angularly condensed hydrocarbons are carcinogenically active which show an energy difference between their highest filled and some empty electron molecular orbitals to be identical with the energy difference between the two filled energy bands of the proteins (3.23 \( \pm 0.19 \text{ eV} \)). His interpretation for this fact is that in the transition complex formed by the molecules of the protein and of the hydrocarbon there may be a possibility for the hydrocarbon molecule to take up an electron from the protein, if the energy difference between the energy bands equals that between the energy levels (Chart 1). Consequently, a conduction via positive hole mechanism occurs in the protein, and the appearance of the conduction produces carcinogenesis by some as yet unknown mechanism.

In connection with Chart 1 it should be mentioned that no proof has been given by Mason for the equality of the energy of the highest filled MO of the hydrocarbons to the energy of the band No. 1 of the protein, but by assuming this equality he had attained a criterion for the carcinogenic activity of angularly condensed hydrocarbons.

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**TABLE 1**

**THE POSITION OF ENERGY BANDS IN EV**

<table>
<thead>
<tr>
<th>Band</th>
<th>(ev)</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.00-0.13</td>
<td>Doubly filled</td>
</tr>
<tr>
<td>2</td>
<td>3.17-3.48</td>
<td>Doubly filled</td>
</tr>
<tr>
<td>3</td>
<td>6.48-6.60</td>
<td>Entirely empty</td>
</tr>
</tbody>
</table>

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\(^1\) C. A. Coulson, private communication.
which was in good agreement with experimental data.

Evidence for the assumption of Mason concerning the formation of the transition complex hydrocarbon-protein has been given by some investigations carried out with C\textsuperscript{14} isotopes (6, 32). It is notable that Mason himself did not exclude the possibility of the formation of direct complexes between the carcinogenic hydrocarbons and the nucleotide bases. The same concept was also mentioned by A. and B. Pullman (29).

On the other hand, according to the results of recent investigations, it is probable that in the mechanism of carcinogenesis the deoxyribonucleic acid, and not the protein molecule, is playing the most important role (20, 21). As is well known, Watson and Crick (8, 40, 42) have constructed a model for the stereo structure of the DNA molecule, with the aid of which a satisfactory explanation could be given for the results of the x-ray diffraction investigations of the DNA (13, 14, 41, 43). According to this model the nucleotide bases of the DNA are placed perpendicular to the axis of the double, right-handed helix of the DNA molecule and are parallel to each other in a distance of 3.36 A. Since according to this model a complete turn of the helix consists of ten bases, the bases placed above each other are distorted by 36° relative to one another. Chart 2 shows schematically the stereo model of the DNA molecule.

**The Electronic Structure of the DNA**

According to the x-ray investigations the adenine, guanine, thymine, and cytosine bases occurring in DNA all have planar structures (an exception is guanine, in which the N atom of the amino group stands out from the plane of the ring by 0.11 A), and the internuclear distances fall between the values characteristic for pure single and pure double bonds (1, 2, 15, 16, 25). One has to assume on this basis that in these molecules delocalized π-electron systems are present, tending to the whole rings. On this assumption A. and B. Pullman have calculated the molecular orbitals of the individual nucleotide bases and their energies with the aid of the simple LCAO MO method (27, 28). We are performing the same computations using six \( a_\iota \) and \( b_{ij} \) integral values instead of the four values used by them.

The existence of the interaction between the π-electrons of the nucleotide bases superimposed parallel to one another (Chart 3) was already assumed a few years ago for the interpretation of the anomalous spectroscopic behavior of the DNA (19, 24); however, no quantitative computations have yet been carried out to evaluate the amount of the interaction.

For an estimation of the amount of this interaction, the computation of the quantum mechanical overlap integrals between the molecular orbitals of the superimposed nucleotide bases appeared to be most useful. The determination of the values of the overlap integrals,

\[
S_\alpha,\beta = \int \psi_\alpha (2p_\iota) \psi_\beta (2p_\iota) \, d\tau ,
\]

between the atoms C-C, C-N, and N-N at a distance of 3.36 A from each other has been carried
The computation of these values has been accomplished by the aid of the $\psi(2p_\sigma)$ and $\psi(2p_\pi)$ Slater's atomic wave functions. From Table 2 it appears obvious that the value of the C–C overlap integral between neighboring rings (second column) is more than 10 per cent of the value of the C–C overlap integral within one ring (third column) and about 15 per cent of the C–N overlap integral within one ring (second column). From this it can be stated that the electron overlap between the rings must not be neglected. It is to be noted that Evans and Gergely have assumed a $\pi$-type interaction between the atoms N and O of the adjacent polypeptide chains in the mentioned computation of the protein molecule. In the case of the N–O distance of 2.65 Å assumed there, the overlap integral becomes

$$S^\pi_{N,O} = \int \psi_N(2p_\sigma) \psi_O(2p_\pi) \, d\tau$$

This value is about one-seventh of the C–C and about one-third of the C–N overlap integrals between different nucleotide bases.

Details of the computation of the integral values shown in Table 2 are presented in another paper (18), which also contains the computation of the overlap integrals between the approximate lowest LCAO molecular orbitals of the superimposed bases of purine-purine, pyrimidine-pyrimidine, purine (l)-pyrimidine (u) and pyrimidine (l)-purine (u). In this computation the distortion of the nucleotide bases of 36° relative to each other has also been taken into account. The overlap integrals between the molecular orbitals proved to be of the same order of magnitude by this method as the values given in Table 2; however, their values for these four cases show considerable deviations from one another. This shows that different amounts of $\pi$-electron interaction belong to different sequences of nucleotide bases. The importance of this fact from a genetic point of view and other biological consequences to be expected are considered in the paper mentioned above (18).

The knowledge of all the LCAO MO values of the individual nucleotide bases will make it possible to determine the interaction between the individual bases more exactly than was done in the calculation sketched above.

Assuming a $\pi$-electron interaction through the hydrogen bonds connecting the adenine-thymine and guanine-cytosine base pairs of DNA, A. and B. Pullman have calculated the LCAO MO energies of these base pairs too, regarding these pairs as unique $\pi$-electron systems (19). The obtained molecular orbital energies are presented in Table 3.

In Table 3 the negative figures of the levels determined as a first step. Their values, together with C–C and C–N $\pi$-type overlap integral values in one ring (Chart 4),

$$S^\pi_{A,B} = \int \psi_A(2p_\pi) \psi_B(2p_\pi) \, d\tau,$$ (2)

computed for comparison, are presented in Table 2.

### TABLE 2

<table>
<thead>
<tr>
<th>Values of Overlap Integrals between Atomic Wave Functions</th>
<th>$S^\pi_{A,B}$</th>
<th>$S^\pi_{A,B}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R = 3.38 Å)</td>
<td>(R = 3.38 Å)</td>
<td></td>
</tr>
<tr>
<td>C–C</td>
<td>0.03210</td>
<td>0.20380</td>
</tr>
<tr>
<td>C–N</td>
<td>0.01527</td>
<td>0.21576</td>
</tr>
<tr>
<td>N–N</td>
<td>0.00815</td>
<td></td>
</tr>
</tbody>
</table>

*The second column of Table 2 refers to the overlap between atoms located in two different superimposed bases. The third column refers to the overlap between atoms located in the same ring.

The DNA double helix is right-handed; thus, a direction is determined, and so the "lower" (l) and "upper" (u) side of the macromolecule can be defined.
noted by roman numerals give the energies of the two lowest antibonding orbitals ($\beta$ is a negative value); and the positive values at the levels denoted by arabic numbers are the energies of the bonding orbitals. Both base pairs, adenine-thymine and guanine-cytosine, contain 24 mobile $\pi$-electrons. Therefore, all the bonding orbitals are filled by two electrons with opposite spins (29). In a DNA macromolecule in consequence of the interaction of the $\pi$-electron systems of the adjacent parallel base pairs, a broadening of these energy levels to energy bands is to be expected.

The formation of energy bands of reasonable width from the energy levels of interacting systems requires two conditions to be fulfilled: (a) There must be a large enough interaction between the systems under consideration, and (b) the energy levels of the interacting systems must differ from one another only slightly. In the DNA macromolecule the first condition is much more likely to obtain than in the protein molecule. This is understandable from a comparison of the values of the overlap integrals between the interacting systems in the two cases (see Table 3 and equation [3]).

In the case of the protein molecule, Evans and Gergely (12) have found a band width of 0.13 ev for the first band, 0.26 ev for the second one, and 0.12 ev for the third, empty band. If one takes the value of 2.8 ev for $\beta$ (the C–C resonance integral in benzene) as was done by Mason (22), these band widths in protein are 0.046 $\beta$, 0.093 $\beta$, and 0.043 $\beta$, respectively. Since the interaction between the adjacent nucleotide bases is larger than that between the polypeptide chains, it seems probable that, in DNA, energy levels with larger energy differences than the widths of the energy bands of protein can form an energy band. We take 0.093 $\beta$, the width of the second filled band in protein, as the criterion for the energy difference between different energy levels to form a band. With this assumption we obtain a qualitative band structure for DNA.

When one considers base pairs instead of single bases, the DNA “one-dimensional crystal” consists of only two repeating units, the adenine-thymine and the guanine-cytosine units. If one takes into account a DNA molecule which is built up of only adenine-thymine pairs, the application of the above criterion yields, as can be seen in Table 3, a band structure with eight filled bands; and the two lowest antibonding orbitals also form a band. These bands are indicated on the left side of the table. The same band structure can be qualitatively derived for a hypothetical DNA molecule which consists of guanine-cytosine units only. These bands are indicated on the right side of the table.

In a real DNA molecule, however, the two units are mixed up with each other. Applying again the above criterion of 0.093 $\beta$ for the energy differences, we get a band structure with five filled bands, and the lowest antibonding orbitals of the two base pairs also forming a common band (Chart 5). These bands are indicated in the middle of the table where the arrows are connecting those orbitals which can form bands. The levels not used in this combination have not fulfilled our criterion for forming a band, and so they either occur as single levels between the bands or perturb in some way the other bands.

After the completion of our present calculations on the LCAO MO values and energies of the single nucleotide bases, we intend to calculate also the MO values of the base pairs with our $a_i$ and $\beta_i$ parameter values. On the basis of the results of these calculations we want to determine, quantitatively also, the positions of the energy bands of DNA.

**The Effect of Radiations on the Electronic Structure of DNA**

In the nucleotide bases and in the protein molecule the $\pi$-electrons are furnished by the same type of atoms, by the atoms C, N, and O. However,
as has been shown above, the values of the overlap integrals between the nucleotide bases proved to be larger than the value of the \( \pi \)-electron overlap integral between the pair of atoms N–O at a distance of 2.65 Å from each other, which is characteristic for the amount of the interaction between the individual polypeptide chains in the model of Evans and Gergely. As a consequence of this, the energy bands of DNA are expected to be somewhat wider than the bands of the protein molecule. This interaction between the nucleotide bases, however, though larger than the interaction between the polypeptide chains, is not sufficient to cause the overlap of the energy bands. Therefore, also in the case of DNA, the highest bonding energy band is entirely filled, and the lowest antibonding band remains empty, since the bonding MO's of the individual nucleotide base pairs are completely filled and no electrons had been left for the antibonding orbitals (29). Consequently, the molecule (at least the ideal one without lattice defects and impurities) is insulator in its ground state and becomes a conductor only by excitation of electrons and the accompanying positive hole mechanism or by the positive hole mechanism concurring with ionization.

The energy differences between the highest occupied and lowest unoccupied MO's of the nucleotide base pairs are 1.00 \( \beta \) for the guanine-cytosine pair and 1.39 \( \beta \) for the adenine-thymine pair (Table 3). The energy difference between the lowest empty and the highest filled band of DNA on the basis of the data reported in Table 3 is expected to be 1.25 \( \beta \). Applying again the value of 2.8 ev for \( \beta \), one finds the width of the forbidden band between the valency band and the conduction band to show a value of about 3.5 ev. This value will depend to a certain degree on the composition of the various DNA molecules, and, since the amount of the interaction between the nucleotide bases varies with their sequence even at a given composition (18), it depends on the sequence of the nucleotide bases too. This variation, however, will probably be only an insignificant one. Consequently, the interpretation given by Mason for the cancerous effect of radiations (namely, the assumption that, when a protein molecule becomes a conductor by exciting an electron from the valency band to the conduction band, the mobility of this electron may stand in some connection with the occurrence of cancer) can be applied not only to the protein but also to the DNA molecule. It must be noted that this estimated value, 3.5 ev, for the width of the forbidden band in DNA agrees better with the energy threshold, 3.4 ev, for the cancer-inducing radiation than the value given by the energy bands in protein, i.e., 3.0 ev. So, when a radiation of sufficient energy attains the DNA molecule, this molecule may also become a conductor by the excitation of an electron into the conduction band.

**A Possible Interpretation for the Mechanism of the Effect of Carcinogens on the Basis of the Electronic Structure of DNA**

The width of the forbidden band between the two highest filled energy bands of DNA will, according to the data at our disposal, probably become considerably smaller than the value of about 3 ev found in proteins. The individual nucleotide bases, however, and the base pairs possess bonding MO's (27–29), the energy differences of which do not show too large a deviation from the value of 1.10 \( \beta \)–1.18 \( \beta \) given by Mason for the level difference as a criterion for the carcinogenic activity of the hydrocarbons. On the basis of this it can be expected that the DNA macromolecule will also have such non-neighboring bands, the energy differences of which are identical to the energy difference between the highest bonding and any antibonding orbital of the carcinogenic hydrocarbon. As mentioned before, no evidence had been given by Mason that the energies of the highest occupied MO's of the carcinogenic hydrocarbons were identical with the energy of the lowest filled \( \pi \)-electron band of the protein. It is, therefore, conceivable that these levels coincide with some (not necessarily with that just below the highest band) bonding energy band of DNA as sketched, for example, in Chart 5.

Carcinogenic hydrocarbons, if brought into interaction with the \( \pi \)-electron system of the DNA as assumed by Mason (22, 23) and by A. and B. Pullman (29) are thus probably able to take over electrons from the DNA molecule in the manner shown in Chart 5 (or in some other way), and thus the DNA will become a conductor by ionization in this way. Further, we can also assume that there is a direct interaction only between the carcinogen and the protein part of the nucleoprotein (32), but that there is also some interaction between the \( \pi \)-electron systems of the protein and of the DNA molecule in the nucleoprotein. In this case the DNA may become conducting by the carcinogen through the intervention of the protein, as shown in Chart 6.

After the determination of the energy bands of DNA we intend to return to a more detailed investigation of this problem. It may, however, be stated here that most probably Mason's mechanism of the effect of the carcinogenic hydrocar-
bons may be applied in a convenient manner not only to the protein but also to the DNA molecule.

**Polarization of Excited or Ionized DNA Molecules by the Effect of Field Strength**

There remains still the question of how the beginning of carcinogenesis relates to the electron mobility in DNA induced by the effect of radiation or a carcinogenic compound. According to our opinion, this problem can be approached by taking into consideration the possibility of the existence of strong local electric fields inside the cell. Such fields may arise, for instance, from the presence of dipolar molecules but may also be caused by many other circumstances (local differences in the ion concentration, proximity of other macromolecules with electric charge, etc.). Since, as has been shown, the DNA molecule in its ground state (at least the ideal molecule without any defect) is most probably an insulator, the static electric field is able to polarize it only by means of deformation of the charge cloud of the individual nucleotide bases. Quite another situation occurs, however, when the DNA becomes conducting by the effect of carcinogens or radiation. Then the field, if its direction corresponds to the direction of the axis of the macromolecule, is able to produce a migration of the $\pi$-electrons and by this to polarize the molecule (Chart 7). Thus, a statistical probability exists for a net electric charge to appear on the ends of an excited or ionized DNA molecule, depending on the partition of the directions of the axes of the macromolecules.

The DNA molecule, however, according to the Watson-Crick model does not consist of one helix but of two helices with common axis. A further question is, what happens in the other helix while one of the helices becomes conducting by the effect of radiation or carcinogens and the field strength present polarizes the excited half-molecule. By examining this question we have again to take into account that through the H-bonds an interaction exists in DNA between the electron systems of the base-pairs connected with the H-bonds—i.e., the base-pairs, adenine-thymine and guanine-cytosine, may be considered as having united delocalized electron systems (29). Consequently, it is more exact to state that the delocalized $\pi$-electron systems belong to the double helices and not to the single ones. In this way, if an excitation of an electron occurs by the effect of radiation or an ionization occurs by a carcinogen at any half of the double helix, the whole double helix becomes conducting. Both molecule parts will therefore be polarized by the electric field present (Chart 8).

There may also arise the question whether an exciton, i.e., a $\pi$-electron of the DNA excited by radiation, is or is not so quickly recombining that the charge cannot attain the ends of the macromolecule. However, by assuming an electric field strong enough in the direction of the molecule axis, the quick recombination does not seem probable, because the electric field separates the electrons and positive holes from each other by ac-
accelerating them in opposite directions, and so they are not able to recombine in a direct way. Thus, if there are not present too many electronic traps, it can be expected that an electron in the conduction band is able to cover the distance of 15μ (corresponding to the length of a large DNA particle) without recombining.

**The Influence of Polarization of the Double Helix in DNA on the Duplication Mechanism of the DNA**

It is known that, according to Watson and Crick, the duplication of the DNA begins by the unwinding of the two helices, and then the corresponding supplementary chains are built to the two separated helices. The sequence of bases in the newly built chain is thus unambiguously determined by the sequence of the nucleotide bases in the original DNA helix through the adenine-thymine, guanine-cytosine correlations. This process can be repeated any number of times. One should note that, besides this semi-conservative mechanism (in the first daughter generation the half parts of the two double helices consist of the old DNA helices and the other halves are newly built), a conservative mechanism (where the double helix remains together, so forming the pattern for the new DNA helix), and a dispersive one (where the original DNA molecule suffers many breaks in cross-direction and so by breaking into smaller chains the two new double helices will be built up of parts of the old one distributed at random in the two helices), has been assumed (9). The experimental data available are not yet sufficient to make an unambiguous decision among these three possibilities (9, 44); however, the semi-conservative mechanism of Watson-Crick seems to be the most probable one, at least for the simple case of the DNA duplication within one cell without genetic recombination (38, 44). At the same time, it is supposed that even in the case of any other duplication mechanism a separation of the double helix would occur in some phase of the duplication process (44).

The energy required for the rupture of a pair of bases may be estimated as follows. The base-pair adenine-thymine contains an H-bond of the type N—H...N and another of the type N—H...O, while in the pair guanine-cytosine an N—H...N and two N—H...O bonds occur. The energy of the N—H...N type H-bond is 1.9 kcal/mole, while that of the N—H...O bond is 2.0 kcal/mole when the O atom is bound with a double bond to a C atom (39). The aforesaid delocalization energy occurring in consequence of the π-electron interaction between the individual nucleotide-bases is according to the computations of A. and B. Pullman (29) for the case of the adenine-thymine base pair 3.2 kcal/mole, and for the guanine-cytosine pair 4.2 kcal/mole. Finally, the calculations of Levinthal and Crane (9, p. 703) give 0.3 kcal/mole for the mechanical unwinding energy for each pair of bases. By a summation of these values the necessary energy for the rupture of the base-pair adenine-thymine becomes thus

$$\Delta E_{A-T} = 6N-N + 6N-H + 6O + 6deloc. + 6mech. \approx 1.9 + 2.0 + 3.2 + 0.3 = 7.4 \text{ kcal/mole},$$

and in the case of the guanine-cytosine pair

$$\Delta E_{G-C} = 6N-N + 4N-H + 4O + 6deloc. + 6mech. \approx 1.9 + 4.0 + 4.2 + 0.3 = 10.4 \text{ kcal/mole}.$$
of some external effect, the ends of the chain take up some energy.

The process may be started, however, even without any external effect which exerts its influence on the ends of the double helix, if—in the manner described above—charges of identical sign are built up at the ends of the two chains. If one assumes that the DNA molecule became polarized by the effect of radiation or of carcinogenic compounds, charges of the magnitude $e_0/2$ and of identical sign are situated at the ends of the chains. If the center of gravity of these charges is approximately in the center of the pyrimidine ring or, respectively, in the midpoint of that C-C bond which is in annelation in the purine ring,

and if one takes, according to the literature (30), 8.00 A as the distance of the N-H...N bond connecting the rings, the distance between the centers of gravity of the two charges becomes 6.70 A (see Chart 9). With these values the potential energy of the repulsion between the two nucleotide bases becomes

$$V = \frac{(e_0/2)^2}{r} = \frac{4.8 \cdot 10^{-20}}{4 \cdot 6.7 \cdot 10^{-8}}$$

$$= 8.6 \cdot 10^{-13} \text{erg} \approx 12.5 \text{ kcal/mole}.$$  

The value obtained in this way agrees well enough with the above given energy required for the rupture of the guanine-cytosine base-pair. On account of the rough approximations applied at this estimation this means, of course, only that, if we put one elementary charge on a base-pair, the potential energy of the occurring repulsion agrees in order of magnitude with the energy required for the rupture of the base-pair. This shows that the polarization of the DNA chain ends occurring from the effect of radiation or of a carcinogen probably might induce the duplication mechanism even without any external effect on the end of the chains. It is to be noted that the conception of electric forces playing a role in the process of cell multiplication has already been assumed. It is indeed generally assumed that electric forces are playing an essential role in the separation of cell nuclei at mitosis (17).

A Possible Relation between the Polarization of DNA and the Formation of Tumors

There remains, of course, the question what is the reason for the occurrence of a macroscopic tumor, when in consequence of excitation or ionization caused by radiation or by a carcinogen a single DNA molecule duplicates in an instant which is not determined by the cooperation of the whole organism. Of course, we cannot undertake the task of finding an unambiguous answer to this question, but we will attempt to suggest two possible ways for the approximation of this problem.

On the one hand, attention has to be drawn to the fact that, if through the known mechanism of some external effect, the ends of the chain take up some energy.

The possible relation between the polarization of DNA and the formation of tumors is important. The electric charges at the ends of DNA might influence the stability of the base-pairs and the configuration of the DNA molecule. Consequently, the $\pi$-electron interaction between them and the other parts of the DNA molecule have to be interrupted or at least diminished to a large extent (Chart 10). After the elimination of the interaction, however, the electric charges of the chain-ending base-pairs are not capable of recombining any more at any other point of the DNA. The re-
maining charge may, therefore, cause an excess of charge in each of the two double helices formed in the duplication process, and these can be newly polarized by the effect of the local electric fields within the cell by the mentioned mechanism. According to our opinion there is, therefore, a finite probability, especially in the case of ionization, that a "hit" of a single photon or carcinogen molecule on a DNA molecule may induce not only one, but more, duplication cycles. Further attention should be paid to the fact that in reality not only a single hit reaches a single DNA molecule in a single cell, but many molecules of DNA of many cells can be excited or ionized by the effect of radiation or of the carcinogen, and also one individual DNA molecule can also get more hits. One may assume in this way that in the cells of some tissue a great number of new DNA molecules can appear in an instant, which is not determined by the growth regulation of the organism and is therefore undesired. This can lead to the mitosis of these cells. Further, it is possible that this change, occurring at an undesired instant, might induce a series of such irreversible biochemical reactions in the tissue in question, which converts these cells from normal ones into tumor cells.

On the other hand, a recent assumption of Burch (3) suggests the beginning of cancer formation by radiation in any cell or cells capable of becoming cancerous, by their receiving two such hits at two different instances, which cause two specific chromosome breaks. An explanation for the mechanism of the chromosome break was given by Butler (4) by assuming that, in the chromosome fibril, which is the morphological unit of the chromosome (31), the relatively weak electrostatic bond between the stick-shaped DNA and nucleohistone molecule forming the chromosome fibrils, which are placed on top of one another, may split off by the effect of radiation, and this causes the chromosome breaking. The probability of the particle's being hit just at this weak bond appears, however, to be a very small one, and no explanation is given by Butler for the question how the effect of a hit at another part of the macromolecule would be able to attain the place of this bond. If the polarization of the ends of the DNA molecule by radiation occurs in the above-treated way, one may understand that the radiation might achieve a dissociation of the electrostatic chain-ending bonds and with this also a chromosome breaking (Chart 11). The phenomenological theory of Burch based on statistical considerations and our own conceptions based on quantum chemical considerations, as well as on the theory of solids, may complement each other in this way.

To support our hypothesis we are continuing our investigations of the electronic structure of DNA. When our present computations for the determination of the MO's of the individual nucleotide-bases and their energies are accomplished, we intend to determine the interaction between individual nucleotide bases more exactly. This will be carried out with the construction of new MO's extended to two superimposed bases. These new MO's will thus be formed by the linear combination of the MO's of the individual bases (LCMO). By a better knowledge of the interaction it will be rendered possible to determine the π-electron energy bands of the DNA. On the other hand, preparations have been made to approach the validity of the hypothesis from an experimental point of view by investigating the behavior of cultures of cancerous tissues placed into the electrostatic field with different field strengths for different periods. The preliminary results have shown a sharp difference between the behavior of cultures placed in the electrostatic field and outside of it, greatly supporting our hypotheses.

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