QUANTUM MECHANICS AND BIOLOGY

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I should like to begin by saying that I feel very diffident about speaking on the subject which the organizers of this Conference invited me to discuss with you. What I have to say will inevitably be limited by the extreme superficiality of my acquaintance with modern biochemistry and biophysics. The only apology which I can offer for being here at all is that I feel, in common with most scientists, that it is a good thing for workers in quite different fields to meet occasionally and compare notes so as to discover whether the methods of one discipline can usefully be applied to the problems of another. It will soon become apparent to you that my opinions on the usefulness of quantum mechanics to biologists are decidedly conservative; but if these opinions are not generally shared, perhaps at least they will provoke discussion.

The thesis which I want to develop in the next few minutes will seem to many of you to be rather pedestrian. Briefly I want to suggest that for many years to come the student of living matter will have much more need for an understanding of physical chemistry than for a knowledge of quantum mechanics. However much one may marvel at the variety and versatility of living things, it cannot be denied that all organisms are in one sense physico-chemical machines. Ingenious and baffling as their structure and function may seem to be, it is therefore proper, in attempting to understand them, to compare their component parts with those inanimate systems which the physical chemist now understands more or less thoroughly. It is true that a full understanding of physical chemistry itself requires some knowledge of quantum mechanics, and that some physico-chemical phenomena are more obviously "quantum-mechanical" than others; but when all is said and done, the greater part of physical chemistry rests upon ideas and methods which are intelligible without *explicit* reference to the quantum theory; an outstanding example of what I mean is the kinetic study of reaction mechanisms.

From the point of view of the physical chemist the processes which take place in living matter—or for that matter in the test tube—may be divided into those which involve radiation and those which do not. This distinction is useful because "quantum effects" are only noticeable when the quanta of energy exchanged between different parts of a system are large compared to kT. With two exceptions, however, all the processes occurring in living matter can take place in the dark. I will have something to say later about photosynthesis, but in the meantime let us consider the tremendous range of phenomena in which radiation is essentially unimportant. Apart from vision, *all* the processes which occur in animal tissues may be classed as 'dark reactions'. These include respiration and glycolysis, protein synthesis, the polymerisation of sugars to glycogen, the synthesis of lipoproteins from fatty acids, the synthesis of nucleic acids and all the processes of active and passive transport which are involved in physiological function. The same applies to plants, except for the vital act of photosynthesis, which is essentially a mechanism for producing ATP and other sources of chemical power from non-reactive starting materials. Briefly then, one may expect photosynthesis, retinal sensitivity and bioluminescence to be the only phenomena for which classical ideas should be seriously inadequate, though this is not to deny that in one sense all physico-chemical phenomena are quantum-mechanical in nature.

Let us now consider in turn a few areas of biophysical chemistry, to see how well this thesis bears detailed examination. Perhaps the most complex problems which have yet been successfully tackled by biophysical methods are those of nerve conduction and muscular contraction. The brilliant research which has been done in these fields has relied successfully upon classical physico-chemical concepts such as membrane potential and ionic permeability. One may obviously ask how a lipid membrane manages to distinguish so unerringly between sodium ions and potassium ions, but in order to answer such a question it would be much better to study the permeability of artificial membranes than to engage in quantum-mechanical calculations on the electronic structures of the alkali metal ions. In any case, such questions may safely be left on one side; the physiologist's problem is to describe biological phenomena in terms of physico-chemical laws, not to interpret chemistry in terms of theoretical physics.

Turning to biochemistry proper, we find the same general situation. One of the most impressive achievements of biochemistry has been to unveil the successive stages in carbohydrate metabolism, both the building up of sugars and polysaccharides from water and carbon dioxide and their breakdown by respiration and glycolysis. The individual steps in carbohydrate metabolism are, of course, catalysed by specific enzymes, whose structure and mode of action is generally unknown; the mapping out of the Krebs cycle and the Calvin cycle has not, however, required ideas any more quantum mechanical than those which are familiar to the pure organic chemist who is interested in reaction mechanisms.

Perhaps this is the point at which to mention a concept which has been found very useful in biochemical discussions, namely that of the "energy-rich bond." The casual observer might get the impression that energy-rich bonds were peculiar to living matter, and that the cell possessed some special faculty for harnessing quantum-mechanical forces. Nowadays we smile at the concept of a "vital force" governing the growth of living matter, but a few years ago it seemed that this force was coming back into biochemistry under an assumed name. The organically-minded biochemist now realizes of course that the energy-rich bond is nothing new; it is merely the link between the two parts of an acid anhydride or a pseudo-acid anhydride, and its high free energy originates in the electronic reorganization which accompanies its hydrolysis. Again one might enquire as to the electronic structures of the molecular species involved, but such a question would lie strictly within the province of the organic chemist, working in collaboration with his theoretically-minded colleagues.

One of the areas of investigation in which appeal has occasionally been made to quantum mechanics is the detailed mechanism of enzyme activity. Regarded as chemical catalysts the enzymes are extremely remarkable both in their efficiency and their specificity. It is most tempting to suppose that enzyme action exhibits some feature which is without parallel in the inorganic world. One might envisage strange forces of a quantum-mechanical nature guiding the substrate towards the prosthetic group, where the atoms are deftly rearranged by some sort of tunnel effect. But when a biochemist begins to use quantum-mechanical language in this nebulous way, we may justifiably suspect that he is talking nonsense. All the forces between atoms and molecules are "quantum-mechanical" in origin; but dispersion forces have long since ceased to mystify the physical chemist, and he is quite familiar with interactions of other kinds as well, even if he is not always in a position to assess them quantitatively. There was, I remember, some discussion a few years ago about the possible occurrence of long-range quantum-mechanical forces between enzymes and their substrates. It was, however, perfectly right that such a hypothesis should be treated with reserve, not only because of the flimsiness of the experimental evidence but also because of the great difficulty of reconciling such an idea with the general theory of intermolecular forces. In this instance perhaps quantum machanics did serve the biologist in a distinctly negative way. But to return to enzyme action: although enzyme specificity is still a largely unsolved problem, we are rapidly learning more about the way in which the prosthetic group of an enzyme induces chemical changes in the adsorbed substrate. The elegant work of Wang on model enzymes is helping to dispel the aura of mystery which has surrounded these catalysts, and one should be thankful that the nerve gases have contributed something useful to science by helping us to understand the mode of action of cholinesterase. But this increase in understanding is coming mainly from the study of model enzymes and from experiments on enzyme inhibition, rather than from quantum-mechanical developments.

To say all this is not to deny that there are some problems in enzyme chemistry on which quantum mechanics has indirectly shed some light, for example the role of metal atoms in the prosthetic groups of certain enzymes. Until recently the biochemist could scarcely hope to understand the function of the iron atom in haemoglobin, and why molybdenum rather than magnesium occurs in nitrogen-fixing enzymes. To most questions of this kind the answers are still lacking but now at least we begin to see the lines along which we should think about them. Theoretical inorganic chemistry has made great strides in the last 10 years, and this has happened largely as a result of the application of quantum mechanics. We now understand very much better than a few years ago the individual properties of the transition elements and their characteristic habits in forming coordination complexes. The student of enzyme kinetics can therefore profit greatly from the study of modern coordination chemistry. But on the whole he is unlikely to encounter phenomena which are without parallel in the much simpler chemistry of non-living matter. I say 'on the whole' because it is always unwise to under-estimate the ingenuity of the living cell; but modern inorganic chemistry already abounds with such a wealth of diverse phenomena that there are plenty of analogies to consider before one need resort to special hypotheses in order to account for the mechanism of enzyme action.

There is one special class of biochemical event which has recently received much discussion in quantum-mechanical terms. This is the process of electron transfer which underlies the sequence of reactions involved in respiration. It is not known exactly how ATP synthesis is coupled with carbohydrate oxidation but it has nevertheless been possible to unravel in some detail the sequence of oxidative processes which occur in the respiratory cycle. Broadly speaking, one finds that respiration occurs through a well-ordered series of redox couples, well-ordered in the sense that the cell succeeds in avoiding chemical short-circuits in which free energy would be degraded directly into heat. Two problems must be distinguished. The first is to interpret the equilibrium and rate constants for each of the redox couples considered in isolation; this should be regarded as a straightforward if difficult physico-chemical problem. The second problem concerns the safety mechanisms which prevent the oxidized form of a couple high up the scale from reacting with the reduced form of a couple lower down. In order to understand this one must not only know the fine details of each reaction mechanism, but also discover exactly how the respiratory enzymes are arranged in the mitochondrion. Purely theoretical considerations are not likely to be of much use in this connection until we know a great deal more about the anatomy of the cell than we do at present.

Is there any value, then, in quantum-mechanical calculations on such entities as the co-enzymes, riboflavin and DPNH? Speaking personally I think that such calculations have some value in connection with the first sort of problem that I have just mentioned, namely the free energy of reaction between two partners of a redox couple considered in isolation. Usually, however, such theoretical researches merely serve to interpret what is already known; if one needs an accurate value for a redox potential, it is best to measure it directly by a polarographic experiment. This situation is, of course, not peculiar to the chemistry of living matter; it is very rare even in pure chemistry for the theoretician to outpace the experimentalist in a prediction about chemical reactivity. But the function of theory is not to compete with observation; it is to provide concepts which the experimenter can use in interpreting his measurements, and in planning new experiments.

Like all dogmatic statements, what I have just said about electron transfer demands some qualification. There comes to mind an enzyme reaction which has impressed almost all biochemists who have thought about it. It is notoriously difficult in the test tube to convert atmospheric nitrogen into ammonia, but the nitrogen-fixing bacteria achieve this feat in the dark at room temperature. The recent work at the DuPont laboratories and elsewhere suggests, moreover, that the nitrogen-fixing enzyme achieves the reduction of molecular nitrogen to ammonia in a single stroke. This conclusion is necessarily tentative, but careful examination reveals no trace of any stable intermediate between N_2 and NH_3. If this is indeed the case, no fewer than 6 electrons must be supplied to the nitrogen molecule either simultaneously or in very rapid succession, and there is no obvious analogy for such a drastic reduction in ordinary chemistry. It looks as if one must have something like a stack of electron-donating systems which can together act as an electron reservoir to which access is abnormally rapid. Such a system would be as "quantum-mechanical" as anything one is likely to meet in living matter, but even so, one is likely to gain more understanding of such systems by studying solid-state physics rather than meditating upon the principles of quantum mechanics, if you will allow the distinction. Physical analogies, where they can be found, are almost always more illuminating than abstract mathematical theory.

One might venture similar comments on the extensive work which has been done in applying the methods of quantum chemistry to the problem of carcinogenesis. Cancer is one of the worst scourges of our time and it might be thought inappropriate to criticize any work which has stimulated experiment in this branch of medical research and suggested correlations between chemical structure and carcinogenic activity. But quantum-mechanical calculations on organic molecules should not be regarded as a substitute for experimental studies of their chemical properties; even the best calculations on molecules are still very crude and inaccurate. Furthermore, as we learn more and more about the cell it becomes increasingly clear that carcinogenic activity can scarcely be a function only of the properties of the carcinogen. Would it be fair to compare the quantum-mechanical approach to carcinogenesis with an attempt to discover the mechanism of a watch by studying in great detail the shapes and sizes of those probes which were most effective in upsetting its mechanism? Actually, of course, the situation is not quite so hopeless as this comparison suggests: it has been astutely pointed out that one particular type of carcinogen is very much the same shape and size as one of the base pairs in DNA. Strong evidence is accumulating that acridine can penetrate the DNA helix for this reason, disordering the sequence of genetical information; but this hypothesis, if correct, can scarcely be described as a quantum-mechanical one in any but the most general sense.

It is now time to turn to those biochemical processes which involve radiation in an essential way. The most important of these is the act of photosynthesis, upon which the whole of life is ultimately founded. Scarcely less important from our selfish point of view is the photo-sensitivity of the retinal tissues of the eye, which in the higher animals is the most highly developed of all the sense organs. Of much less importance, but none the less facinating, is the phenomenon of bioluminescence, and finally there are one or two photochemical processes such as the production of skin pigments under the influence of ultraviolet light.

The work of Calvin and others has brought into sharp focus the mechanistic problem presented by photosynthesis. The first biochemical achievement of the chloroplast is to produce a reducing agent and an oxidizing agent by the dissociation of water. Somehow or other the photons falling on the chloroplast must be collected, transferred to one or more active sites and there trapped so that the energy of the light cannot pass back to its origin and be degrated uselessly into heat. Let us consider in turn the various elementary steps. There is good structural evidence that the chlorophyll molecules are packed together, presumably in a roughly crystalline arrangement so that every photon which is absorbed produces a collective excitation in the aggregate. Such excitations are familiar to the solid state physicist, and it is known that they can pass quickly through a crystal. One may think of such an 'exciton' as an excited electron closely associated with its complementary hole, so that as long as the exciton remains undissociated it cannot carry any electric charge through the crystal. One would therefore suppose that somewhere in the molecular array there are electron traps at which the excited electron can be detached from the positive hole with which it is paired; there must also be places in the array at which the positive hole can be utilised by oxidizing some entity with a readily available electron. One would expect these two kinds of trap to be separated in space, in order to avoid direct interaction between them, or that at least each kind of trap must be able to react rapidly with some other chemical agent as soon as it has trapped an excited electron or been oxidized by a positive hole. The subsequent chemical events have the character of ordinary redox reactions, and will, presumably, present no special novel kinetic features.

There can be little doubt, surely, that the photo-synthetic act is that biological problem to which quantum mechanics has made, and is likely to make, the most useful contribution. The 'exciton' is a thoroughly quantum-mechanical concept, and one which is vital to discussion of energy transfer. There are, of course, many unsolved problems in this field, for example: do the migrating excitons have singlet or triplet character? Is one exciton capable of producing a chemical change, or does the chloroplast have to store several quanta, possibly in the form of triplet molecules, before there is enough energy for reaction to occur? Such problems have been carefully studied both by spectroscopists and by photochemists, and there is every hope that they will soon be solved; but the question could not be asked in these terms if quantum mechanics had not provided the basic concepts needed for their formulation. Here at last, then, we find quantum mechanics coming into its own, and being of real service to the biochemist and biophysicist.

In some ways there is a resemblance between the problem of photosynthesis and that of retinal photosensitivity. Just as in photosynthesis there is the problem as to how the energy absorbed by the visual pigments is transported to the active sites in the rods and cones, and the hypothesis of exciton migration commends itself by analogy with the properties of ordinary crystals. An additional question which arises in the study of vision concerns the mechanism of bleaching of the visual pigments; these pigments are transformed and subsequently regenerated in a manner which has no parallel in green plants. Such secondary problems are, however, most likely to yield to attack by ordinary photochemical methods rather than to purely theoretical analysis.

There is no time, and I have not the competence, to enlarge upon the detailed biochemistry of retinal action or bioluminescence. It does seem, however, that one may hope to understand these phenomena in terms of the behaviour of simpler systems which have received thorough study. Photoinduced cis-trans isomerisation is a familiar event in photochemistry, and so is chemiluminescence. Although it must be admitted that we have still much to learn about the chemistry of the excited state, there is nothing intrinsically mysterious about the production of light in a highly exergonic reaction, or the rearrangement of a group of atoms supplied with a large quantum of energy. It is, therefore, the physical chemist to whom the biologist should first turn for advice about such happenings, rather than to the student of quantum mechanics.

At the risk of slight irrelevance I might mention very briefly one other photochemical process which occurs in living tissues, namely the production and protective action of melanin. Melanin has the interesting property that it exhibits a strong electron resonance signal, which indicates the presence of many unpaired electrons. Chemically speaking melanin has the structural features of a partially reduced polyquinone, and it has been argued that this type of system should exhibit the properties of a semiconductor. In its optical properties melanin conforms very closely with such a description, and so one might feel inclined to embark upon a quantum-mechanical investigation of its biological function. I suspect however that such an endeavour might distract attention from the possibility that a reservoir of free electrons might be particularly well suited to the destruction of the harmful free radicals which are known to be formed when ultra-violet light falls upon aqueous systems. It seems quite likely that the essential function of melanin is not to directly absorb the ultraviolet light, but to convert hydrogen atoms and hydroxyl radicals into the harmless hydrogen and hydroxyl ions.

At the outset of this lecture I issued a warning that my views were conservative, and I may even seem to be a right-wing fanatic. What I have tried to do is not, however, to put up a barbed wire fence between biology and quantum mechanics, but only to suggest that apart from vision and photosynthesis biological processes may be more easily understood by reference to ordinary physical chemistry rather than by a purely theoretical onslaught. In the remaining few minutes I would like to supplement this thesis with some rather more positive remarks.

In studying biological systems, modern physical techniques have proved to be of immense value. Of these techniques the various forms of spectroscopy have made a pre-eminent contribution to our detailed knowledge, second only to what has been achieved by X-ray crystallography and electron microscopy. There are one or two spectroscopic phenomena which have rendered special service to the biophysicist, and two of these deserve individual mention.

In studies on DNA and its phase transformations much use has been made of the remarkable decrease in ultraviolet absorption which accompanies the ordering of the base pairs in a regular stack. This phenomenon, called "hypochromism," was at the same time an immense help and also a source of embarrassment to the molecular biologist, as it seemed to contradict Beer's law in circumstances where this law ought to hold. Until this paradox could be resolved, the results of these experiments could not properly be understood. The paradox has now been resolved by Tinoco, by the methods of quantum-mechanical perturbation theory. Tinoco showed very clearly that the interactions which cause van der Waals attraction should produce optical side-effects of exactly the kind observed in DNA, and his work has placed measurements of hypochromism on a sound theoretical foundation. Here then is a clear case in which quantum mechanics has helped to clarify an obscure experimental situation, although such situations must undoubtedly occur in ordinary molecular crystals as well, and might have been found there first if they had been looked for.

Another example of the same general kind is the optical rotation of helical polypeptides, though this is now a fairly old story. The question was whether one could use the observed optical rotation of a polypeptide as a clue to its mode of coiling or folding. This problem was essentially a theoretical one, and was successfully tackled by Kirkwood and Moffitt, using quantum-mechanical methods. For α helices they calculated an optical rotation quite close to what is observed in some synthetic polypeptides, and although measurements of optical activity have still a rather limited application, they provide a useful supplement to other studies on biological polymers.

The same may be said of infra-red studies. It is sometimes possible to determine the orientation of small vibrating groups such as C=O or N—H by polarized infra-red studies. But in order to interpret measurements of this type one must refer back to the physical theory of light absorption, which is based directly upon quantum mechanics. It may therefore be said that what we know about the structures of polypeptides and other materials is founded in part upon quantum-mechanical principles, although the absorption of infra-red radiation is not a phenomenon of much biological importance.

Time will permit me to refer only to one other sort of spectroscopic technique, namely electron spin resonance and nuclear magnetic resonance, which provide us with new ways of looking into the cell and examining its contents. We can, for example, establish the presence of unpaired electrons in certain tissues by electron spin resonance; we can identify the electronic state of the metal atom in a porphyrin, and, it will be remembered, the orientation of the haem groups in haemoglobin was first determined by electron spin resonance. Nuclear magnetic resonance has so far not yielded such fruitful results, but it promises to give useful information about the motion of molecules in the cytoplasm and possibly also about simple rapid reactions such as proton exchange. There is no reason, of course, to imagine that magnetic resonance is a phenomenon of any biological importance whatever; quantum mechanics does, however, impinge at this point on biology in providing the physical concepts which are needed for interpreting magnetic resonance experiments.

Before concluding, I shall touch upon one other problem, of a more philosophical character. Can one establish any logical connection between the physical Principle of Uncertainty and our mental experience of free choice? On this intellectually hazardous issue I merely want to make one comment, for which I am indebted to Professor D. M. MacKay. MacKay has pertinently remarked that at ordinary temperatures even a classical system is subject to random thermal fluctuations. The precision with which we can ascertain the state of a molecular system is therefore limited just as seriously by Brownian motion as by quantum effects, so that it would be misleading to think that the Uncertainty Principle blurs a physical description which could otherwise be completely precise. Briefly, then, *if* unpredictability has anything to do with free will, we should pay more attention to thermal noise than to quantum-mechanical effects.

The time has come for me to summarize my main theme. What I have been trying to say is not that quantum mechanics is irrelevant to biological phenomena, but that the illumination afforded by quantum mechanics is like indirect lighting, reflected from physical chemistry and solid state physics. Most of the phenomena confronting the biologist differ only in complexity and not in essence from those which occur in non-living matter, and it is usually more fruitful to look for simple physical analogies than to engage in purely quantum mechanical discussions. This is not to deny the importance of quantum mechanics in providing the theoretical background to spectroscopic measurements, but we must be careful to avoid the aura of mystery which can so easily be produced by reference to "quantum-mechanical effects."