Atomic Physics and Vital Activities*

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THE success of the two discussions held during the current year has justified the policy which decided that such discussions should be organised from time to time. In particular they are valuable when they tempt distinguished workers from abroad to visit the Society as contributors to debate. In the discussion on the structure of atomic nuclei opened by Lord Rutherford, the revelation of new experimental results and of their great significance gave a dramatic character to the meeting. The atomic nucleus for a long time had seemed to be an impregnable fortress; but missiles of high destructive power have been gradually contrived by almost magical skill in the army of attack, and the fortress, in spite of its formidable potential barrier, is crumbling.

It is interesting for the spectator to realise how much is learnt by the commanders of the attack from the nature of the missiles (parts of itself) with which the fortress replies to the bombardment. One cannot help recalling the sense of progressive accomplishment which was conveyed in Lord Rutherford's opening address, as for example when he dealt with the nuclear origin of the γ -rays. Nor can one forget moments of actual excitement as when, recalling a twelve years' old prophecy of his own respecting the probable existence of neutrons, he referred to Dr. J. Chadwick's recent success in producing these entities (of which the mass is unity and the charge zero) by bombarding beryllium with α -particles from polonium. Exciting again was the account of the striking results obtained also in the Cavendish Laboratory by J. D. Cockcroft and E. T. S. Walton, who constructed an apparatus capable of providing a steady stream of protons, of energy up to 600,000 volts, and successfully employed the stream in the disintegration of the lithium nucleus.

It is not unjustifiable to say that before the moment of Cockcroft and Walton's success, man did not know how to release atomic energy on his own initiative, whereas now, though doubtless in a limited sense, he possesses that power. At the same time, the phenomenon of transmutation seems to be at hand in full reality. The occasion of this discussion cannot fail to stand out as of much significance in the annals of the Royal Society and in the history of Great Britain's contribution to science.

The second discussion dealt with the growth of knowledge at a different level of present accomplishment; but with phenomena that are very significant. It was concerned with recent studies of the nature and properties of those highly active catalysts—the enzymes—the presence of which in each living unit converts a system, which without

them would be static, into an organism which is so characteristically dynamic. Anyone who reads in succession the records of these two discussions as found in our *Proceedings*, will perhaps be tempted to wonder how soon, if ever, intellectual concepts, based upon the phenomena which were the subject of the first, are fated to invade, and perhaps revolutionise thought in the great field of which the second covered part. Will the data of atomic physics ultimately illuminate the processes of life?

At present we know nothing to suggest a certain answer. I have indeed met not a few who had a strong *a priori* conviction that life, in some way, in some limited sense at least, makes use of atomic energy; that such ability might indeed be the special stamp of life. Some twelve years ago a distinguished Dutch physiologist, the late Prof. Zwaardemaker, thought he had proved that the weak radioactivity of potassium is an indispensable stimulus to certain vital activities; but the importance of this influence would seem to be at most very small. Even Zwaardemaker did not hold that it conditioned life. Its radioactivity is certainly not the main reason for the indispensability of potassium in living systems.

Certain recent experimental studies, however, seem to have proved that living tissues may be the seat of radiations able to produce effects at a distance, and to suggest that certain activities in one cell of a tissue can thus influence activities in neighbouring cells. It was claimed some time ago by Gurvitsch, a Russian biologist, that when growing cells divide they emit rays which accelerate the processes of division in other cells. The existence of these mitogenetic rays, so called because of the claim mentioned, met at first with general disbelief, and a year ago I might have been disinclined to mention the subject; but work by many during the last year seems to have brought satisfactory proof that chemical reactions in living tissues are indeed accompanied by radiations, and events in one cell may thus influence other cells without material transmission.

The phenomena as described are doubtless related to that of chemiluminescence which many non-biological reactions display, and may perhaps have affinities with the emission of more intensive radiations by specialised cells in the luminiferous organs of animals or by luminiferous bacteria. The much more general invisible radiations under reference have been now studied by physical methods. Their emission from active cells has been (it is claimed) demonstrated by means of Geiger's counter; their wave-length measured, and by methods which I must not stop to describe, their specific spectra in various cases duly mapped. It has even been claimed, for example, that a characteristic spectrum of a radiation from a tetanised muscle is identical with that yielded

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in vitro by a reaction (the breakdown of creatin phosphate) known to occur in active muscle.

Many published statements of this kind must be received with hesitation until fully confirmed; but that activities in living cells may be accompanied by radiations recognisable by physical means is now, I think, a fact which is proved. This alone will certainly lead to many fresh lines of inquiry. It is not yet proved, however, that the phenomena as described are of fundamental importance, or even that they associated with all forms of life.

What, on the other hand, we do know for certain, is that in all living systems in which dynamic events have been adequately studied, the influence of colloidal catalysts is found to be dominant. These catalysts ('enzymes' if you will) exert a specific control over complex chemical reactions, of which the exact co-ordination in time and space is one of the primary characteristics of an organism. It is, I think, difficult to exaggerate the importance to biology, and I venture to say to chemistry no less, of extended studies of enzymes and their action. Of the chemical reactions displayed in an organism few, if any, proceed uncatalysed; while they are reactions so completely and harmoniously organised that all are maintained in complex dynamic equilibrium. If chemical thought is to function with effect in helping towards a description of living systems, it must dwell especially on this chemical co-ordination which, like other aspects of organisation, illustrates that subservience of parts to the whole which characterises an organism.

The organising potentialities inherent in highly specific catalysis have not, I believe, been adequately appraised in chemical thought. The concentration of a catalyst or, alternatively, the extent of its active surface, will determine the velocity of changes due to its influence, but highly specific catalysts determine in addition just what particular materials, rather than any others, shall undergo change. In this respect they are like the living cell itself, for they select from their environment. Finally, the specific catalyst, in virtue of its own intimate structure, determines which among possible paths the course of change shall follow. It has directive powers. Even in a cell juice, or in an extract from living tissues from which all cell structure is absent, experiment has shown that a group of contributory reactions, including syntheses, may proceed in due and just sequence and so lead to the same end result as is normally reached in the intact living system. A striking degree of organisation may indeed be attained in such preparations under the directive influence of the more soluble enzymes derived from the cell or tissue. Much more than must a structured colloidal system, like the intact cell, in which a number of catalysts with such controlling powers are present in circumstances exactly adjusted to a final result, be one in which reactions are conditioned and organised to a high degree without the aid of unknown or any other influences.

I do not expect that all will feel able to admit as much as I myself would like to claim, namely, that the control of events by intracellular enzymes, exerted in the specialised colloidal apparatus of the cell, by itself secures the status of the cell as a system which can maintain itself in dynamic equilibrium with its environment. I am not denying for a moment that the cell has esoteric qualities which may call for organising influences of a greatly different kind; exerted maybe at some higher level. It is at any rate sure that the inter-related activity of highly specific catalysts represents a notable device of Nature which has supported during the course of evolution those dynamic manifestations which characterise living things.

Prof. R. Willstätter, together with members of his school, has done much to advance our knowledge of these agencies. I have sometimes heard it suggested that the advance in question, from a chemical point of view at any rate, represents a relative failure, apparently because no enzyme has yet been isolated in a state to conform with the classical criteria of 'purity'. If this be the reason for any suggestion of failure, there is surely some misunderstanding. Isolation, individualisation and purity are words which, if used at all in this domain, may well need to be given meanings differing not a little from those which are applicable in classical organic chemistry. Few will doubt to-day that the specific influence of a catalyst is due to its specific structure. All indications, however, point to the circumstance that the active structure of an enzyme is supported by a colloidal 'carrier' which stabilises it. It is indeed likely that in very many cases, if not in all, the active catalytic mechanism is a specific configuration at part of the surface of a colloidal particle, or, alternatively, part of a structural surface in the histological sense. If so, we should no more expect to isolate them in a pure state than so to isolate the active areas on a catalytic metallic surface.

It is true that enzymic activity may be displayed by agencies which are not all strictly of one type. It is not unlikely that in certain cases the specifically active groups may be inherent in the structure of a complex but relatively stable molecule, such as that of an exceptional protein. Cases are known indeed in which a protein many times recrystallised retains specific enzymic activity; in one such case at least it has been shown that the protein structure can be to a large extent destroyed without disappearance of the activity. Crystallisation in such a case does not yield an entity which would reveal its active structure to the ordinary methods of organic chemistry. What is essential for enzyme studies at their present stage is an assurance that a single entity alone is responsible for this or that observed activity. To this end the technique developed by the school of Willstätter has greatly helped. While we are waiting for the knowledge which may ultimately yield, on lines acceptable to current chemical thought, a method for characterising these exceptional entities as

units, the actual configuration which confers activity on this or that enzyme can be, and in many cases no doubt soon will be, determined by indirect methods.

I would like now to illustrate a little further the nature of current progress in animal biochemistry by a reference to investigations dealing with related, but somewhat different aspects of control of dynamic phenomena in living tissues.

From the researches published during the year I might select many to show that efforts to disentangle the complexities of these phenomena can in their own way be as profitable as any branch of chemical endeavour. I think it will be more useful, however, to refer more particularly to one research which is typical of many in respect of its methods and its success. In this the investigator approached on new lines a fundamental problem which for the last sixty years has been the subject of speculation, and no less of experiments which up to a point were informative. The problem was to discover the nature of the final chemical steps which lead to the production of urea in the animal body. That the mammalian liver can convert ammonium carbonate into urea has been many times experimentally proved, and it is equally sure that ammonia and, of course, carbon dioxide are continuously produced in metabolism. Therefore most of us have long been content to believe that urea arises by the direct removal of the elements of water from the molecule of ammonium carbonate.

That urea does indeed arise in the liver by a synthesis from ammonia and carbon dioxide remains certain; but the research under reference, brilliantly carried out by Krebs, of Freiburg-im-Breisgau, has shown that its production is on no such simple lines as those mentioned. It calls for a mechanism involving a most interesting interplay among activated molecules. The facts as revealed have just that degree of unexpectedness—if I may use the phrase—which was to be expected in a biochemical phenomenon. I often find myself compelled to assert that though biochemical events are, of course, limited by chemical possibilities, they are not safely to be predicted by chemical probabilities, even when these are strong. That is why experimental biochemistry must remain an independent scientific discipline.

The essential results of Krebs's research include consideration of the molecular structure of three biological substances: ornithin, citrullin and arginin. In the presence of ammonia and carbon dioxide, and when activated by agencies in the hepatic tissue, ornithin is converted into citrullin which, as a ureido-acid, already carries the carbamide structure. Urea does not arise directly from this, however; another stage intrudes. Citrullin takes up another molecule of ammonia (with elimination of water as at the first stage) and the structure of arginin with its guanidin grouping is thus established. Now arginin is the normal substrate for the well-studied and very active hepatic enzyme, arginase; and under its

influence the guanidin group is hydrolysed. Urea thereupon splits off from the arginin molecule and ornithin is reproduced. The sequence is then re-established.

Urea is thus produced continuously from the ammonia which arises in the deamination of the amino acids of protein, and from the carbon dioxide of metabolic oxidations in general, but on lines which may seem strangely complex. It would be too much to say at present that this is the only line of origin for urea in the body, but we know now that it is the main line. In maintaining the sequence of reactions, ornithin can function in minute amounts; acting therefore essentially as a catalyst. The nature of the relations involved in this mechanism is characteristic of the living cell.

In another respect this example illustrates the nature of current biochemical studies. The data were obtained by the methods of micro-analysis and only a few milligrams of hepatic tissue were employed in individual experiments. Yet the results were consistent and reproducible and experimental errors well under control. The high accuracy to be obtained in ordinary organic analysis by micro methods is now well recognised, but it is becoming clear that technique is so developing that kinetic studies can be made equally accurate on a similar scale. To studies of living systems this offers advantages which cannot be overestimated.

One further point: it is becoming more and more a matter for confidence that when tissues with cells intact are quickly removed from the animal after its death and placed straightway in a fluid medium of carefully proved adequacy, it only remains to provide an adequate supply of oxygen which shall reach each unit of the tissue, to secure the continuance of the events which had been proceeding *in vivo*. Indeed we are gaining sufficient knowledge of the requirements of such excised tissues to justify the claim that the course of metabolism observed in them during extensive periods of survival need differ in no way from the normal.

We can proceed, then, from the study of tissue extracts in which it is easy to deal with the kinetics of isolated reactions, each determined by its appropriate catalyst, to studies of other tissue extracts, made with discrimination, in which the progress of a variety of reactions retains not a little of the organisation which characterised them during life, and thence to other studies in which we follow the kinetics of reactions controlled by the intact and still living tissues or cells. Thus and otherwise has biochemistry escaped from the dilemma voiced in earlier dogma, namely, that since chemical methods must at the very moment of their application convert the living into the dead, they can do nothing to elucidate the dynamic events of life. The escape is more real than may seem on a superficial view, and especially real perhaps to those who are themselves applying modern chemical methods in the biological field.