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SOME CHEMICAL ASPECTS OF LIFE[1]

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I

THE British Association returns to Leicester with assurance of a welcome as warm as that received twenty-six years ago, and of hospitality as generous. The renewed invitation and the ready acceptance speak of mutual appreciation born of the earlier experience. Hosts and guests have to-day reasons for mutual congratulations. The association on its second visit finds Leicester altered in important ways. It comes now to a city duly chartered and the seat of a bishopric. It finds there a center of learning, many fine buildings which did not exist on the occasion of the first visit and many other evidences of civic enterprise. The citizens of Leicester, on the other hand, will know that since they last entertained it the association has celebrated its centenary, has four times visited distant parts of the Empire and has maintained unabated through the years its useful and important activities.

In 1907 the occupant of the presidential chair was, as you know, Sir David Gill, the eminent astronomer who, unhappily, like many who listened to his address, is with us no more. Sir David dealt in that address with aspects of science characterized by the use of very exact measurement. The exactitude which he prized and praised has since been developed by modern physics and is now so great that its methods have real esthetic beauty. In contrast I have to deal with a branch of experimental science which, because it is concerned with living organisms, is in respect of measurement on a different plane. Of the very essence of biological systems is an ineludable complexity, and exact measurement calls for conditions here unattainable. Many may think, indeed, though I am not claiming it here, that in studying life we soon meet with aspects which are non-metrical. I would

[1] The presidential address before the British Association for the Advancement of Science, Leicester, September 6.

have you believe, however, that the data of modern biochemistry, which will be the subject of my remarks, were won by quantitative methods fully adequate to justify the claims based upon them.

Though speculations concerning the origin of life have given intellectual pleasure to many, all that we yet know about it is that we know nothing. Sir James Jeans once suggested, though not with conviction, that it might be a disease of matter, a disease of its old age! Most biologists, I think, having agreed that life's advent was at once the most improbable and the most significant event in the history of the universe, are content for the present to leave the matter there.

We must recognize, however, that life has one attribute that is fundamental. Whenever and wherever it appears the steady increase of entropy displayed by all the rest of the universe is then and there arrested. There is no good evidence that in any of its manifestations life evades the second law of thermodynamics, but in the downward course of the energy-flow it interposes a barrier and dams up a reservoir which provides potential for its own remarkable activities. The arrest of energy degradation in living nature is indeed a primary biological concept. Related to it, and of equal importance, is the concept of organization.

It is almost impossible to avoid thinking and talking of life in this abstract way, but we perceive it, of course, only as manifested in organized material systems, and it is in them we must seek the mechanisms which arrest the fall of energy. Evolution has established division of labor here. From far back the wonderfully efficient functioning of structures containing chlorophyll has, as every one knows, provided the trap which arrests and transforms radiant energy —fated otherwise to degrade—and so provides power for nearly the whole living world. It is impossible to believe, however, that such a complex mechanism was associated with life's earliest stages. Existing organisms illustrate what was perhaps an earlier method. The so-called autotrophic bacteria obtained energy for growth by the catalyzed oxidation of materials belonging wholly to the inorganic world; such as sulfur, iron or ammonia, and even free hydrogen. These organisms dispense with solar energy, but they have lost in the evolutionary race because their method lacks economy. Other existing organisms, certain purple bacteria, seem to have taken a step towards greater economy, without reaching that of the green cell. They dispense with free oxygen and yet obtain energy from the inorganic world. They control a process in which carbon dioxide is reduced and hydrogen sulfide simultaneously oxidized. The molecules of the former are activated by solar energy which their pigmentary equipment enables these organisms to arrest.

Are we to believe that life still exists in association with systems that are much more simply organized than any bacterial cell? The very minute filter-passing viruses which, owing to their causal relations with disease, are now the subject of intense study, awaken deep curiosity with respect to this question. We can not yet claim to know whether or not they are living organisms. In some sense they grow and multiply, but, so far as we yet know with certainty, only when inhabitants of living cells. If they are nevertheless living, this would suggest that they have no independent power of obtaining energy and so can not represent for us the earliest forms in which life appeared. At present, however, judgment on their biological significance must be suspended. The fullest understanding of all the methods by which energy may be acquired for life's processes is much to be desired.

In any case every living unit is a transformer of energy, however acquired, and the science of biochemistry is deeply concerned with these transformations. It is with aspects of that science that I am to deal, and if to them I devote much of my address my excuse is that since it became a major branch of inquiry biochemistry has had no exponent in the chair I am fortunate enough to occupy.

As a progressive scientific discipline it belongs to the present century. From the experimental physiologists of the last century it obtained a charter, and, from a few pioneers of its own, a promise of success; but for the furtherance of its essential aim that century left it but a small inheritance of facts and methods. By its essential or ultimate aim I myself mean an adequate and acceptable description of molecular dynamics in living cells and tissues.

II

When this association began its history in 1831 the first artificial synthesis of a biological product was, as you will remember, but three years old. Primitive faith in a boundary between the organic and the inorganic which could never be crossed was only just then realizing that its foundations were gone. Since then, during the century of its existence, the association has seen the pendulum swing back and forth between frank physicochemical conceptions of life and various modifications of vitalism. It is characteristic of the present position and spirit of science that sounds of the long conflict between mechanists and vitalists are just now seldom heard. It would almost seem, indeed, that tired of fighting in a misty atmosphere each has retired to his tent to await with wisdom the light of further knowledge. Perhaps, however, they are returning to the fight disguised as Determinist and Indeterminist, respectively. If so, the outcome will be of great interest. In any case I feel fortunate in a belief that what I have to say will not, if rightly appraised, raise the old issues. To claim, as I am to claim, that a description of its active chemical aspects must contribute to any adequate description of life is not to imply that a living organism is no more than a physicochemical system. It implies that at a definite and recognizable level of its dynamic organization an organism can be logically described in physicochemical terms alone. At such a level indeed we may hope ultimately to arrive at a description which is complete in itself, just as descriptions at the morphological level of organization may be complete in themselves. There may be yet higher levels calling for discussion in quite different terms.

I wish, however, to remind you of a mode of thought concerning the material basis of life, which, though it prevailed when physicochemical interpretations were fashionable, was yet almost as inhibitory to productive chemical thought and study as any of the claims of vitalism. This was the conception of that material basis as a single entity, as a definite though highly complex chemical compound. Up to the end of the last century and even later the term "protoplasm" suggested such an entity to many minds. In his brilliant presidential address at the association's meeting at Dundee twenty-two years ago, Sir Edward Sharpey-Schafer, after remarking that the elements composing living substances are few in number, went on to say: "The combination of these elements into a colloid compound represents the physical basis of life, and when the chemist succeeds in building up this compound it will, without doubt, be found to exhibit the phenomena which we are in the habit of associating with the term 'life.'" Such a compound would seem to correspond with the "protoplasm" of many biologists, though treated perhaps with too little respect. The presidential claim might have seemed to encourage the biochemist, but the goal suggested would have proved elusive, and the path of endeavor has followed other lines.

So long as the term "protoplasm" retains a morphological significance, as in classical cytology, it may be even now convenient enough, though always denoting an abstraction. In so far, however, as the progress of metabolism with all the vital activities which it supports was ascribed in concrete thought to hypothetical qualities emergent from a protoplasmic complex in its integrity or when substances were held to suffer change only because in each living cell they are first built up, with loss of their own molecular structure and identity, into this complex, which is itself the inscrutable seat of cyclic change, then serious obscurantism was involved.

Had such assumptions been justified the old taunt that when the chemist touches living matter it immediately becomes dead matter would also have been justified. A very distinguished organic chemist, long since dead, said to me in the late eighties: 'The chemistry of the living? That is the chemistry of protoplasm; that is superchemistry; seek, my young friend, for other ambitions."

Research, however, during the present century, much of which has been done since the association last met in Leicester, has yielded knowledge to justify the optimism of the few who started to work in those days. Were there time, I might illustrate this by abundant examples; but I think a single illustration will suffice to demonstrate how progress during recent years has changed the outlook for biochemistry. I will ask you to note the language used thirty years ago to describe the chemical events in active muscle and compare it with that used now. In 1895 Michael Foster, a physiologist of deep vision, dealing with the respiration of tissues, and in particular with the degree to which the activity of muscle depends on its contemporary oxygen supply, expounded the current view which may be thus briefly summarized. The oxygen which enters the muscle from the blood is not involved in immediate oxidations, but is built up into the substance of the muscle. It disappears into some protoplasmic complex on which its presence confers instability. This complex, like all living substance, is to be regarded as incessantly undergoing changes of a double kind, those of building up and those of breaking down. With activity the latter predominates, and in the case of muscle the complex in question explodes, as it were, to yield the energy for contraction. "We can not yet trace," Foster comments, "the steps taken by the oxygen from the moment it slips from the blood into the muscle substance to the moment when it issues united with carbon as carbonic acid. The whole mystery of life lies hidden in that process, and for the present we must be content with simply knowing the beginning and the end." What we feel entitled to say to-day concerning the respiration of muscle and of the events associated with its activity requires, as I have suggested, a different language, and for those not interested in technical chemical aspects the very change of language may yet be significant. The conception of continuous building up and continuous breakdown of the muscle substance as a whole has but a small element of truth. The colloid muscle structure is, so to speak, an apparatus, relatively stable even as a whole when metabolism is normal, and in essential parts very stable. The chemical reactions which occur in that apparatus have been followed with a completeness which is, I think, striking. It is carbohydrate stores distinct from the apparatus (and in certain circumstances also fat stores) which undergo steady oxidation and are the ultimate sources of energy for muscular work. Essential among successive stages in the chemical breakdown of carbohydrate which necessarily precede oxidation is the intermediate combination of a sugar (a hexose) with phosphoric acid to form an ester. This happening is indispensable for the progress of the next stage, namely, the production of lactic acid from the sugar, which is an anaerobic process. The precise happenings to the hexose sugar while in combination with phosphoric acid are from a chemical standpoint remarkable. Very briefly stated they are these! One half of the sugar molecule is converted into a molecule of glycerin and the other half into one of pyruvic acid. Now with loss of two hydrogen atoms glycerin yields lactic acid, and, with a gain of the same pyruvic acid also yields lactic acid. The actual happening then is that hydrogen is transferred from the glycerin molecule while still combined with phosphoric acid to the pyruvic acid molecule with the result that two molecules of lactic acid are formed.[2] The lactic acid is then, during a cycle of change which I must not stop to discuss, oxidized to yield the energy required by the muscle.

But the energy from this oxidation is by no means directly available for the mechanical act of contraction. The oxidation occurs indeed after and not before or during a contraction. The energy it liberates secures, however, the endothermic resynthesis of a substance, creatin phosphate, of which the breakdown at an earlier stage in the sequence of events is the more immediate source of energy for contraction. Even more complicated are these chemical relations, for it would seem that in the transference of energy from its source in the oxidation of carbohydrate to the system which synthesizes creatin phosphate, yet another reaction intervenes, namely, the alternating breakdown and resynthesis of the substance adenyl pyrophosphate. The sequence of these chemical reactions in muscle has been followed and their relation in time to the phases of contraction and relaxation is established. The means by which energy is transferred from one reacting system to another has still lately been obscure, but current work is throwing light upon this interesting question, and it is just beginning (though only beginning) to show how at the final stage the energy of the reactions is converted into the mechanical response. In parenthesis it may be noted as an illustration of the unity of life that the processes which occur in the living yeast cell in its dealings with sugars are closely similar to those which proceed in living muscle. In the earlier stages they are identical and we now know where they part company. You will, I think, be astonished at the complexity of the events which underlie the activity of a muscle, but you must remember that it is a highly specialized machine. A more direct burning of the fuel could not fit into its complex organization. I am more particularly concerned to feel that my brief summary of the facts will make you realize how much more definite, how much more truly chemical, is our present knowledge than that available when Michael Foster wrote. Ability to recognize the progress of such definite ordered chemical reactions in relation to various aspects of living activity characterizes the current position in biochemistry. I have chosen the case of muscle, and it must serve as my only example, but many such related and ordered reactions have been studied in other cells and tissues, from bacteria to the brain. Some prove general, some more special. Although we are far indeed from possessing a complete picture in any one case we are beginning in thought to fit not a few pieces together. We are on a line safe for progress.

[2] Lecture by Otto Meyerhof: in press (see *Nature*).

I must perforce limit the field of my discussion, and in what follows my special theme will be the importance of molecular structure in determining the properties of living systems. I wish you to believe that molecules display in such systems the properties inherent in their structure even as they do in the laboratory of the organic chemist. The theme is no new one, but its development illustrates as well as any other, and to my own mind perhaps better than any other, the progress of biochemistry. Not long ago a prominent biologist, believing in protoplasm as an entity, wrote, "But it seems certain that living protoplasm is not an ordinary chemical compound, and therefore can have no molecular structure in the chemical sense of the word." Such a belief was common. One may remark, moreover, that when the development of colloid chemistry first brought its indispensable aid towards an understanding of the biochemical field, there was a tendency to discuss its bearing in terms of the less specific properties of colloid systems, phase-surfaces, membranes, and the like, without sufficient reference to the specificity which the influence of molecular structure, wherever displayed, impresses on chemical relations and events. In emphasizing its importance I shall leave no time for dealings with the nature of the colloid structures of cells and tissues, all important as they are. I shall continue to deal, though not again in detail, with chemical reactions as they occur within those structures. Only this much must be said. If the colloid structures did not display highly specialized molecular structure at their surface, no reactions would occur; for here catalysis occurs. Were it not equipped with catalysts, every living unit would be a static system.

With the phenomena of catalysis I will assume you have general acquaintance. You know that a catalyst is an agent which plays only a temporary part in chemical events which it nevertheless determines and controls. It reappears unaltered when the events are completed. The phenomena of catalysis, though first recognized early in the last century, entered but little into chemical thought or enterprise, till only a few years ago they were shown to have great importance for industry. Yet catalysis is one of the most significant devices of nature, since it has endowed living systems with their fundamental character as transformers of energy, and all evidence suggests that it must have played an indispensable part in the living universe from the earliest stages of evolution.

The catalysts of a living cell are the enzymic structures which display their influences at the surface of colloidal particles or at other surfaces within the cell. Current research continues to add to the great number of these enzymes which can be separated from, or recognized in, living cells and tissues, and to increase our knowledge of their individual functions.

A molecule within the system of the cell may remain in an inactive state and enter into no reactions until at one such surface it comes in contact with an enzymic structure which displays certain adjustments to its own structure. While in such association the inactive molecule becomes (to use a current term) "activated," and then enters on some definite path of change. The one aspect of enzymic catalysis which for the sake of my theme I wish to emphasize is its high specificity. An enzyme is in general adjusted to come into effective relations with one kind of molecule only, or at most with molecules closely related in their structure. Evidence based on kinetics justifies the belief that some sort of chemical combination between enzyme and related molecule precedes the activation of the latter, and for such combinations there must be close correlation in structure. Many will remember that long ago Emil Fischer recognized that enzymic action distinguishes even between two optical isomers and spoke of the necessary relation being as close as that of key and lock.

There is an important consequence of this high specificity in biological catalysis to which I will direct your special attention. A living cell is the seat of a multitude of reactions, and in order that it should retain in a given environment its individual identity as an organism, these reactions must be highly organized. They must be of determined nature and proceed mutually adjusted with respect to velocity, sequence, and in all other relations. They must be in dynamic equilibrium as a whole and must return to it after disturbance. Now if of any group of catalysts, such as are found in the equipment of a cell, each one exerts limited and highly specific influence, this very specificity must be a potent factor in making for organization.

Consider the case of any individual cell in due relations with its environment, whether an internal environment, as in the case of the tissue cells of higher animals, or an external environment, as in the case of unicellular organisms. Materials for maintenance of the cell enter it from the environment. Discrimination among such materials is primarily determined by permeability relations, but of deeper significance in that selection is the specificity of the cell catalysts. It has often been said that the living cell differs from all non-living systems in its power of selecting from a heterogeneous environment the right material for the maintenance of its structure and activities. It is, however, no vital act but the nature of its specific catalysts which determines what it effectively "selects." If a molecule gains entry into the cell and meets no catalytic influence capable of activating it, nothing further happens save for certain ionic and osmotic adjustments. Any molecule which does meet an adjusted enzyme can not fail to suffer change and become directed into some one of the paths of metabolism. It must here be remembered, moreover, that enzymes as specific catalysts not only promote reactions, but determine their direction. The glucose molecule, for example, though its inherent chemical potentialities are, of course, always the same, is converted into lactic acid by an enzyme system in muscle but into alcohol and carbon dioxide by another in the yeast cell. It is important to realize that diverse enzymes may act in succession and that specific catalysis has directive as well as selective powers. If it be syntheses in the cell which are most difficult to picture on such lines we may remember that biological syntheses can be, and are, promoted by enzymes, and there are sufficient facts to justify the belief that a chain of specific enzymes can direct a complex synthesis along lines, predetermined by the nature of the enzymes themselves. I should like to develop this aspect of the subject even further, but to do so might tax your patience. I should add that enzyme control, though so important, is not the sole determinant of chemical organization in a cell. Other aspects of its colloidal structure play their part.

III

It is surely at that level of organization, which is based on the exact coordination of a multitude of chemical events within it, that a living cell displays its peculiar sensitiveness to the influence of molecules of special nature when these enter it from without. The nature of very many organic molecules is such that they may enter a cell and exert no effect. Those proper to metabolism follow, of course, the normal paths of change. Some few, on the other hand, influence the cell in very special ways. When such influence is highly specific in kind it means that some element of structure in the entrant molecule is adjusted to meet an aspect of molecular structure somewhere in the cell itself. We can easily understand that in a system so minute the intrusion even of a few such molecules may so modify existing equilibria as to affect profoundly the observed behavior of the cell.

Such relations, though by no means confined to them, reach their greatest significance in the higher organisms, in which individual tissues, chemically diverse, differentiated function and separated in space, so react upon one another through chemical agencies transmitted through the circulation as to coordinate by chemical transport the activities of the body as a whole. Unification by chemical means must to-day be recognized as a fundamental aspect of all such organisms. In all of them it is true that the nervous system has pride of place as the highest seat of organizing influence, but we know to-day that even this influence is often, if not always, exerted through properties inherent in chemical molecules. It is indeed most significant for my general theme to realize that when a nerve impulse reaches a tissue the sudden production of a definite chemical substance at the nerve ending may be essential to the response of that tissue to the impulse. It is a familiar circumstance that when an impulse passes to the heart by way of the vagus nerve fibers the beat is slowed, or, by a stronger beat, arrested. That is, of course, part of the normal control of the heart's action. Now it has been shown that whenever the heart receives vagus impulses the substance acetyl cholin is liberated within the organ. To this fact is added the further fact that in the absence of the vagus influence, the artificial injection of minute graded doses of acetyl choline so acts upon the heart as to reproduce in every detail the effects of graded stimulation of the nerve. Moreover, evidence is accumulating to show that in the case of other nerves belonging to the same morphological group as the vagus, but supplying other tissues, this same liberation of acetyl choline accompanies activity, and the chemical action of this substance upon such tissues again produces effects identical with those observed when the nerves are stimulated. More may be claimed. The functions of another group of nerves are opposed to those of the vagus group; impulses, for instance, through certain fibers accelerate the heart beat. Again a chemical substance is liberated at the endings of such nerves, and this substance has itself the property of accelerating the heart. We find then that such organs and tissues respond only indirectly to whatever non-specific physical change may reach the nerve ending. Their direct response is to the influence of particular molecules with an essential structure when these intrude into their chemical machinery.

It follows that the effect of a given nerve stimulus may not be confined to the tissue which it first reaches. There may be humeral transmissions of its effect, because the liberated substance enters the lymph and blood. This again may assist the coordination of events in the tissues.

From substances produced temporarily and locally and by virtue of their chemical properties translating for the tissues the messages of nerves, we may pass logically to consideration of those active substances which carry chemical messages from organ to organ. Such in the animal body are produced continuously in specialized organs, and each has its special seat or seats of action where it finds chemical structures adjusted in some sense or other to its own.

I shall be here on familiar ground, for that such agencies exist, and bear the name of hormones is common knowledge. I propose only to indicate how many and diverse are their functions, as revealed by recent research, emphasizing the fact that each one is a definite and relatively simple substance with properties that are primarily chemical and in a derivative sense physiological. Our clear recognition of this, based at first on a couple of instances, began with this century, but our knowledge of their number and nature is still growing rapidly to-day.

We have long known, of course, how essential and profound is the influence of the thyroid gland in maintaining harmonious growth in the body, and in controlling the rate of its metabolism. Three years ago a brilliant investigation revealed the exact molecular structure of the substance—thyroxin—which is directly responsible for these effects. It is a substance of no great complexity. The constitution of adrenalin has been longer known and likewise its remarkable influence in maintaining a number of important physiological adjustments. Yet it is again a relatively simple substance. I will merely remind you of secretin, the first of these substances to receive the name of hormone, and of insulin, now so familiar because of its importance in the metabolism of carbohydrates and its consequent value in the treatment of diabetes. The most recent growth of knowledge in this field has dealt with hormones which, in most remarkable relations, coordinate the phenomena of sex.

It is the circulation of definite chemical substances produced locally that determines during the growth of the individual the proper development of all the secondary sexual characters. The properties of other substances secure the due progress of individual development from the unfertilized ovum to the end of fetal life. When an ovum ripens and is discharged from the ovary a substance, now known as estrin, is produced in the ovary itself, and so functions as to bring about all those changes in the female body which make secure the fertilization of the ovum. On the discharge of the ovum new tissue, constituting the so-called *corpus luteum,* arises in its place. This then produces a special hormone which in its turn evokes all those changes in tissues and organs that secure a right destiny for the ovum after it has been fertilized. It is clear that these two hormones do not arise simultaneously, for they must act in alternation, and it becomes of great interest to know how such succession is secured. The facts here are among the most striking. Just as higher nerve centers in the brain control and coordinate the activities of lower centers, so it would seem do hormones, functioning at, so to speak, a higher level in organization, coordinate the activities of other hormones. It is a substance produced in the anterior portion of the pituitary gland situated at the base of the brain, which by circulating to the ovary controls the succession of its hormonal activities. The cases I have mentioned are far from exhausting the numerous hormonal influences now recognized.

For full appreciation of the extent to which chemical substances control and coordinate events in the animal body by virtue of their specific molecular structure, it is well not to separate too widely in thought the functions of hormones from those of vitamins. Together they form a large group of substances of which every one exerts upon physiological events its own indispensable chemical influence.

Hormones are produced in the body itself, while vitamins must be supplied in the diet. Such a distinction is, in general, justified. We meet occasionally, however, an animal species able to dispense with an external supply of this or that vitamin. Evidence shows, however, that individuals of that species, unlike most animals, can in the course of their metabolism synthesize for themselves the vitamin in question. The vitamin then becomes a hormone. In practise the distinction may be of great importance, but for an understanding of metabolism the functions of these substances are of more significance than their origin.

The present activity of research in the field of vitamins is prodigious. The output of published papers dealing with original investigations in the field has reached nearly a thousand in a single year. Each of the vitamins at present known is receiving the attention of numerous observers in respect both of its chemical and biological properties, and though many publications deal, of course, with matters of detail, the accumulation of significant facts is growing fast.

It is clear that I can cover but little ground in any reference to this wide field of knowledge. Some aspects of its development have been interesting enough. The familiar circumstance that attention was drawn to the existence of one vitamin (B_1 so called) because populations in the East took to eating milled rice instead of the whole grain; the gradual growth of evidence which links the physiological activities of another vitamin (D) with the influence of solar radiation on the body, and has shown that they are thus related, because rays of definite wave-length convert an inactive precursor into the active vitamin, alike when acting on foodstuffs or on the surface of the living body; the fact again that the recent isolation of vitamin C and the accumulation of evidence for its nature started from the observation that the cortex of the adrenal gland displayed strongly reducing properties; or yet again the proof that a yellow pigment widely distributed among plants, while not the vitamin itself, can be converted within the body into vitamin A; these and other aspects of vitamin studies will stand out as interesting chapters in the story of scientific investigation.

In this very brief discussion of hormones and vitamins I have so far referred only to their functions as manifested in the animal body. Kindred substances, exerting analogous functions, are, however, of wide and perhaps of quite general biological importance. It is certain that many microorganisms require a supply of vitamin-like substances for the promotion of growth, and recent research of a very interesting kind has demonstrated in the higher plants the existence of specific substances produced in special cells which stimulate growth in other cells, and so in the plant as a whole. These so-called auxines are essentially hormones. Section B will soon be listening to an account of their chemical nature.

It is of particular importance to my present theme and a source of much satisfaction to know that our knowledge of the actual molecular structure of hormones and vitamins is growing fast. We have already exact knowledge of the kind in respect to not a few. We are indeed justified in believing that within a few years such knowledge will be extensive enough to allow a wide view of the correlation between molecular structure and physiological activity. Such correlation has long been sought in the case of drugs, and some generalizations have been demonstrated. It should be remembered, however, that until quite lately only the structure of the drug could be considered. With increasing knowledge of the tissue structures pharmacological actions will become much clearer.

I can not refrain from mentioning here a set of relations connected especially with the phenomena of tissue growth which are of particular interest. It will be convenient to introduce some technical chemical considerations in describing them, though I think the relations may be clear without emphasis being placed on such details. The vitamin which in current usage is labeled "A" is essential for the general growth of an animal. Recent research has provided much information as to its chemical nature. Its molecule is built up of units which possess what is known to chemists as the isoprene structure. These are condensed in a long carbon chain which is attached to a ring structure of a specific kind. Such a constitution relates it to other biological compounds, in particular to certain vegetable pigments, one of which a carotene, so called, is the substance which I have mentioned as being convertible into the vitamin. For the display of an influence upon growth, however, the exact details of the vitamin's proper structure must be established. Now turning to vitamin D, of which the activity is more specialized, controlling as it does the growth of bone in particular, we have learned that the unit elements in its structure are again isoprene radicals; but instead of forming a long chain as in vitamin A they are united into a system of condensed rings. Similar rings form the basal component of the molecules of sterols, substances which are normal constituents of nearly every living cell. It is one of these, inactive itself, which ultra-violet radiation converts into vitamin D. We know that as stated each of these vitamins stimulates growth in tissue cells. Next consider another case of growth stimulation, different because pathological in nature. As you are doubtless aware, it is well known that long contact with tar induces a cancerous growth of the skin. Very important researches have recently shown that particular constituents in the tar are alone concerned in producing this effect. It is being further demonstrated that the power to produce cancer is associated with a special type of molecular structure in these constituents. This structure, like that of the sterols, is one of condensed rings, the essential difference being that (in chemical language) the sterol rings are hydrogenated, whereas those in the cancer-producing molecules are not. Hydrogenation indeed destroys the activity of the latter. Recall, however, the ovarian hormone estrin. Now the molecular structure of estrin has the essential ring structure of a sterol, but one of the constituent rings is not hydrogenated. In a sense therefore the chemical nature of estrin links vitamin D with that of cancer-producing substances. Further, it is found that substances with pronounced cancer-producing powers may produce effects in the body like those of estrin. It is difficult when faced with such relations not to wonder whether the metabolism of sterols, which when normal can produce a substance stimulating physiological growth, may in very special circumstances be so perverted as to produce within living cells a substance stimulating pathological growth. Such a suggestion must, however, with present knowledge, be very cautiously received. It is wholly without experimental proof. My chief purpose in this reference to this very interesting set of relations is to emphasize once more the significance of chemical structure in the field of biological events.

Only the end results of the profound influence which minute amounts of substances with adjusted structure exert upon living cells or tissues can be observed in the intact bodies of man or animals. It is doubtless because of the elaborate and sensitive organization of chemical events in every tissue cell that the effects are proportionally so great.

It is an immediate task of biochemistry to explore the mechanism of such activities. It must learn to describe in objective chemical terms precisely how and where such molecules as those of hormones and vitamins intrude into the chemical events of metabolism. It is indeed now beginning this task, which is by no means outside the scope of its methods. Efforts of this and of similar kind can not fail to be associated with a steady increase in knowledge of the whole field of chemical organization in living organisms, and to this increase we look forward with confidence. The promise is there. Present methods can still go far, but I am convinced that progress of the kind is about to gain great impetus from the application of those new methods of research which chemistry is inheriting from physics: X-ray analysis; the current studies of unimolecular surface films and of chemical reactions at surfaces; modern spectroscopy; the quantitative developments of photochemistry; no branch of inquiry stands to gain more from such advances in technique than does biochemistry at its present stage. Especially is this true in the case of the colloidal structure of living systems, of which in this address I have said so little.

IV

As an experimental science, biochemistry, like classical physiology, and much of experimental biology, has obtained, and must continue to obtain, many of its data from studying parts of the organism in isolation, but parts in which dynamic events continue. Though fortunately it has also methods of studying reactions as they occur in intact living cells, intact tissues and, of course, in the intact animal, it is still entitled to claim that its studies of parts are consistently developing its grasp of the wholes it desires to describe, however remote that grasp may be from finality. Justification for any such claim has been challenged in advance from a certain philosophic standpoint. Not from that of General Smuts, though in his powerful address which signalized our centenary meeting he, like many philosophers to-day, emphasized the importance of properties which emerge from systems in their integrity, bidding us remember that a part while in the whole is not the same as the part in isolation. He hastened to admit in a subsequent speech, however, that for experimental biology, as for any other branch of science, it was logical and necessary to approach the whole through its parts.

Nor again is the claim challenged from the standpoint of such a teacher as A. N. Whitehead, though in his philosophy of organic mechanism there is no real entity of any kind without internal and multiple relations, and each whole is more than the sum of its parts. I nevertheless find *ad hoc* statements in his writings which directly encourage the methods of biochemistry. In the teachings of J. S. Haldane, however, the value of such methods have long been directly challenged. Some here will perhaps remember that in his address to Section I, twenty-five years ago he described a philosophic standpoint which he has courageously maintained in many writings since. Dr. Haldane holds that to the enlightened biologist a living organism does not present a problem for analysis; it is, *qua* organism, axiomatic. Its essential attributes are axiomatic; heredity, for example, is for biology not a problem but an axiom. "The problem of physiology is not to obtain piecemeal physico-explanations of physiological processes" (I quote from the 1885 address), "but to discover by observation and experiment the relatedness to one another of all the details of structure and activity in each organism as expressions of its nature as one organism." I can not pretend adequately to discuss these views here. They have often been discussed by others, not always perhaps with understanding. What is true in them is subtle, and I doubt if their author has ever found the right words in which to bring to most others a conviction of such truth. It is involved in a world outlook. What I think is scientifically faulty in Haldane's teaching is the *a priori* element which leads to bias in the face of evidence. The task he sets for the physiologist seems vague to most people, and he forgets that with good judgment a study of parts may lead to an intellectual synthesis of value. In 1885 he wrote: "That a meeting-point between biology and physical science may at some time be found there is no reason for doubting. But we may confidently predict that if that meeting-point is found, and one of the two sciences is swallowed up, that one will not be biology." He now claims indeed that biology has accomplished the heavy meal, because physics has been compelled to deal no longer with Newtonian entities but, like the biologist, with organisms such as the atom proves to be. Is it not then enough for my present purpose to remark on the significance of the fact that not until certain atoms were found spontaneously splitting piecemeal into parts, and others were afterwards so split in the laboratory, did we really know anything about the atom as a whole.

At this point, however, I will ask you not to suspect me of claiming that all the attributes of living systems or even the more obvious among them are necessarily based upon chemical organization alone. I have already expressed my own belief that this organization will account for one striking characteristic of every living cell—its ability, namely, to maintain a dynamic individuality in diverse environments. Living cells display other attributes even more characteristic of themselves; they grow, multiply, inherit qualities and transmit them. Although to distinguish levels of organization in such systems may be to abstract from reality it is not illogical to believe that such attributes as these are based upon organization at a level which is in some sense higher than the chemical level. The main necessity from the standpoint of biochemistry is then to decide whether nevertheless at its own level, which is certainly definable, the results of experimental studies are self-contained and consistent. This is assuredly true of the data which biochemistry is now acquiring. Never during its progress has chemical consistency shown itself to be disturbed by influences of any ultrachemical kind.

Moreover, before we assume that there is a level of organization at which chemical controlling agencies must necessarily cease to function, we should respect the intellectual parsimony taught by Occam and be sure of their limitations before we seek for superchemical entities as organizers. There is no orderly succession of events which would seem less likely to be controlled by the mere chemical properties of a substance than the cell divisions and cell differentiation which intervene between the fertilized ovum and the finished embryo. Yet it would seem that a transmitted substance, a hormone in essence, may play an unmistakable part in that remarkable drama. It has for some years been known that, at an early stage of development, a group of cells forming the so-called "organizer" of Spemann induces the subsequent stages of differentiation in other cells. The latest researches seem to show that a cell-free extract of this "organizer" may function in its place. The substance concerned is, it would seem, not confined to the "organizer" itself, but is widely distributed outside, though not in, the embryo. It presents, nevertheless, a truly remarkable instance of chemical influence.

It would be out of place in such a discourse as this to attempt any discussion of the psycho-physical problem. However much we may learn about the material systems which, in their integrity, are associated with consciousness, the nature of that association may yet remain a problem. The interest of that problem is insistent and it must be often in our thoughts. Its existence, however, justifies no prejudgments as to the value of any knowledge of a consistent sort which the material systems may yield to experiment.

V

It has become clear, I think, that chemical modes of thought, whatever their limitation, are fated profoundly to affect biological thought. If, however, the biochemist should at any time be inclined to overrate the value of his contributions to biology or to underrate the magnitude of problems outside his province, he will do well sometimes to leave the laboratory for the field, or to seek even in the museum a reminder of that infinity of adaptations of which life is capable. He will then not fail to work with a humble mind, however great his faith in the importance of the methods which are his own.

It is surely right, however, to claim that in passing from its earlier concern with dead biological products to its present concern with active processes within living organisms, biochemistry has become a true branch of progressive biology. It has opened up modes of thought about the physical basis of life which could scarcely be employed at all a generation ago. Such data and such modes of thought as it is now providing are pervasive, and must appear as aspects in all biological thought. Yet these aspects are, of course, only partial. Biology in all its aspects is showing rapid progress, and its bearing on human welfare is more and more evident.

Unfortunately, the nature of this new biological progress and its true significance is known to but a small section of the lay public. Few will doubt that popular interest in science is extending, but it is mainly confined to the more romantic aspects of modern astronomy and physics. That biological advances have made less impression is probably due to more than one circumstance, of which the chief, doubtless, is the neglect of biology in our educational system. The startling data of modern astronomy and physics, though of course only when presented in their most superficial aspects, find an easier approach to the uninformed mind than those of the new experimental biology can hope for. The primary concepts involved are paradoxically less familiar. Modern physical science, moreover, has been interpreted to the intelligent public by writers so brilliant that their books have had a great and stimulating influence.

Lord Russell once ventured on the statement that in passing from physics to biology one is conscious of a transition from the cosmic to the parochial, because from a cosmic point of view life is a very unimportant affair. Those who know that supposed parish well are convinced that it is rather a metropolis entitled to much more attention than it sometimes obtains from authors of guide-books to the universe. It may be small in extent, but is the seat of all the most significant events. In too many current publications, purporting to summarize scientific progress, biology is left out or receives but scant reference. Brilliant expositions of all that may be met in the region where modern science touches philosophy have directed thought straight from the implications of modern physics to the nature and structure of the human mind, and even to speculation concerning the mind of the Deity. Yet there are aspects of biological truth already known which are certainly germane to such discussions, and probably necessary for their adequacy.

VI

It is, however, because of its extreme importance to social progress that public ignorance of biology is especially to be regretted. Sir Henry Dale has remarked that "it is worth while to consider to-day whether the imposing achievements of physical science have not already, in the thought and interests of men at large, as well as in technical and industrial development, overshadowed in our educational and public policy those of biology to an extent which threatens a one-sided development of science itself and of the civilization which we hope to see based on science." Sir Walter Fletcher, whose death during the past year has deprived the nation of an enlightened adviser, almost startled the public, I think, when he said in a national broadcast that "we can find safety and progress only in proportion as we bring into our methods of statecraft the guidance of biological truth." That statecraft, in its dignity, should be concerned with biological teaching, was a new idea to many listeners. A few years ago the Cambridge philosopher, Dr. C. D. Broad, who is much better acquainted with scientific data than are many philosophers, remarked upon the misfortune involved in the unequal development of science; the high degree of our control over inorganic nature combined with relative ignorance of biology and psychology. At the close of a discussion as to the possibility of continued mental progress in the world, he summed up by saying that the possibility depends on our getting an adequate knowledge and control of life and mind before the combination of ignorance on these subjects with knowledge of physics and chemistry wrecks the whole social system. He closed with the somewhat startling words: "Which of the runners in this very interesting race will win it is impossible to foretell. But physics and death have a long start over psychology and life!" No one surely will wish for, or expect, a slowing in the pace of the first, but the quickening up in the latter which the last few decades have seen is a matter for high satisfaction. But, to repeat, the need for recognizing biological truth as a necessary guide to individual conduct and no less to statecraft and social policy still needs emphasis to-day. With frank acceptance of the truth that his own nature is congruent with all those aspects of nature at large which biology studies, combined with intelligent understanding of its teaching, man would escape from innumerable inhibitions, due to past history and present ignorance, and equip himself for higher levels of endeavor and success.

Inadequate as at first sight it may seem when standing alone in support of so large a thesis, I must here be content to refer briefly to a single example of biological studies bearing upon human welfare. I will choose one which stands near to the general theme of my address. I mean the current studies of human and animal nutrition. You are well aware that during the last twenty years—that is, since it adopted the method of controlled experiment—the study of nutrition has shown that the needs of the body are much more complex than was earlier thought, and in particular that substances consumed in almost infinitesimal amounts may, each in its way, be as essential as those which form the bulk of any adequate dietary. This complexity in its demands will, after all, not surprise those who have in mind the complexity of events in the diverse living tissues of the body.

My earlier reference to vitamins, which had somewhat different bearings, was, I am sure, not necessary for a reminder of their nutritional importance. Owing to abundance of all kinds of advertisement vitamins are discussed in the drawing-room as well as in the dining-room, and also, though not so much, in the nursery, while at present perhaps not enough in the kitchen. Unfortunately, among the uninformed their importance in nutrition is not always viewed with discrimination. Some seem to think nowadays that if the vitamin supply is secured the rest of the dietary may be left to chance, while others suppose that they are things so good that we can not have too much of them. Needless to say, neither assumption is true. With regard to the second indeed it is desirable, now that vitamin concentrates are on the market and much advertised, to remember that excess of a vitamin may be harmful. In the case of that labeled D at least we have definite evidence of this. Nevertheless, the claim that every known vitamin has highly important nutritional functions is supported by evidence which continues to grow. It is probable, but perhaps not yet certain, that the human body requires all that are known.

The importance of detail is no less in evidence when the demands of the body for a right mineral supply are considered. A proper balance among the salts which are consumed in quantity is here of prime importance, but that certain elements which ordinary foods contain in minute amounts are indispensable in such amounts is becoming sure. To take but a single instance: The necessity of a trace of copper, which exercises somewhere in the body an indispensable catalytic influence on metabolism, is as essential in its way as much larger supplies of calcium, magnesium, potassium or iron. Those in close touch with experimental studies continually receive hints that factors still unknown contribute to normal nutrition, and those who deal with human dietaries from a scientific standpoint know that an ideal diet can not yet be defined. This reference to nutritional studies is indeed mainly meant to assure you that the great attention they are receiving is fully justified. No one here, I think, will be impressed with the argument that because the human race has survived till now in complete ignorance of all such details the knowledge being won must have academic interest alone. This line of argument is very old and never right.

One thing I am sure may be claimed for the growing enlightenment concerning human nutrition and the recent recognition of its study. It has already produced one line of evidence to show that nurture can assist nature to an extent not freely admitted a few years ago. That is a subject which I wish I could pursue. I can not myself doubt that various lines of evidence, all of which should be profoundly welcome, are pointing in the same direction.

Allow me just one final reference to another field of nutritional studies. Their great economic importance in animal husbandry calls for full recognition. Just now agricultural authorities are becoming acutely aware of the call for a better control of the diseases of animals. Together these involve an immense economic loss to the farmers, and therefore to the country. Although, doubtless, its influence should not be exaggerated, faulty nutrition plays no small share in accounting for the incidence of some among these diseases, as researches carried out at the Rowett Institute in Aberdeen and elsewhere are demonstrating. There is much more of such work to be done with great profit.

VII

In every branch of science the activity of research has greatly increased during recent years. This all will have realized, but only those who are able to survey the situation closely can estimate the extent of that increase. It occurred to me at one time that an appraisement of research activities in this country, and especially the organization of state-aided research, might fittingly form a part of my address. The desire to illustrate the progress of my own subject led me away from that project. I gave some time to a survey, however, and came to the conclusion, among others, that from eight to ten individuals in the world are now engaged upon scientific investigations for every one so engaged twenty years ago. It must be remembered, of course, that not only has research endowment greatly increased in America and Europe, but that Japan, China and even India have entered the field and are making contributions to science of real importance. It is sure that, whatever the consequences, the increase of scientific knowledge is at this time undergoing a positive acceleration.

Apropos, I find difficulty as to-day's occupant of this important scientific pulpit in avoiding some reference to impressive words spoken by my predecessor which are still echoed in thought, talk and print. In his wise and eloquent address at York Sir Alfred Ewing reminded us with serious emphasis that the command of nature has been put into man's hand before he knows how to command himself. Of the dangers involved in that indictment he warned us; and we should remember that General Smuts also sounded the same note of warning in London.

Of science itself it is, of course, no indictment. It may be thought of rather as a warning signal to be placed on her road: "Dangerous Hill Ahead," perhaps, or "Turn Right"; not, however, "Go Slow," for that advice science can not follow. The indictment is of mankind. Recognition of the truth it contains can not be absent from the minds of those whose labors are daily increasing mankind's command of nature; but it is due to them that the truth should be viewed in proper perspective. It is, after all, war, to which science has added terrors, and the fear of war, which alone give it real urgency—an urgency which must of course be felt in these days when some nations at least are showing the spirit of selfish and dangerous nationalism. I may be wrong, but it seems to me that, war apart, the gifts of science and invention have done little to increase opportunities for the display of the more serious of man's irrational impulses. The worst they do perhaps is to give to clever and predatory souls that keep within the law the whole world for their depredations, instead of a parish or a country as of yore.

But Sir Alfred Ewing told us of "the disillusion with which, now standing aside, he watches the sweeping pageant of discovery and invention in which he used to make unbounded delight." I wish that one to whom applied science and this country owe so much might have been spared such disillusion, for I suspect it gives him pain. I wonder whether, if he could have added to an "Engineer's Outlook" the outlook of a biologist, the disillusion would still be there. As one just now advocating the claims of biology I would much like to know. It is sure, however, that the gifts of the engineer to humanity at large are immense enough to outweigh the assistance he may have given to the forces of destruction.

It may be claimed for biological science, in spite of vague references to bacterial warfare and the like, that it is not of its nature to aid destruction. What it may do towards making man as a whole more worthy of his inheritance has yet to be fully recognized. On this point I have said much. Of its service to his physical betterment you will have no doubts. I have made but the bare reference in this address to the support that biological research gives to the art of medicine. I had thought to say much more of this, but found that if I said enough I could say nothing else.

There are two other great questions so much to the front just now that they tempt a final reference. I mean, of course, the paradox of poverty amidst plenty and the replacement of human labor by machinery. Applied science should take no blame for the former, but indeed claim credit unfairly lost. It is not within my capacity to say anything of value about the paradox and its cure; but I confess that I see more present danger in the case of "Money *versus* Man" than danger present or future in that of the "Machine *versus* Man"!

With regard to the latter it is surely right that those in touch with science should insist that the replacement of human labor will continue. Those who doubt this can not realize the meaning of that positive acceleration in science, pure and applied, which now continues. No one can say what kind of equilibrium the distribution of leisure is fated to reach. In any case an optimistic view as to the probable effects of its increase may be justified.

It need not involve a revolutionary change if there is real planning for the future. Lord Melchett was surely right when some time ago he urged on the upper House that present thought should be given to that future; but I think few men of affairs seriously believe what is yet probable, that the replacement we are thinking of will impose a new structure upon society. This may well differ in some essentials from any of those alternative social forms of which the very names now raise antagonisms. I confess that if civilization escapes its other perils I should fear little the final reign of the machine. We should not altogether forget the difference in use which can be made of real and ample leisure compared with that possible for very brief leisure associated with fatigue; nor the difference between compulsory toil and spontaneous work. We have to picture, moreover, the reactions of a community which, save for a minority, has shown itself during recent years to be educable. I do not think it fanciful to believe that our highly efficient national broadcasting service, with the increased opportunities which the coming of short wavelength transmission may provide, might well take charge of the systematic education of adolescents after the personal influence of the schoolmaster has prepared them to profit by it. It would not be a technical education but an education for leisure. Listening to organized courses of instruction might at first be for the few; but ultimately might become habitual in the community which it would specially benefit.

In parenthesis allow me a brief further reference to "planning." The word is much to the front just now, chiefly in relation with current enterprises. But there may be planning for more fundamental developments; for future adjustment to social reconstructions. In such planning the trained scientific mind must play its part. Its vision of the future may be very limited, but in respect of material progress and its probable consequences science (I include all branches of knowledge to which the name applies) has at least better data for prophecy than other forms of knowledge.

It was long ago written, "Wisdom and knowledge shall be stability of Thy times." Though statesmen may have wisdom adequate for the immediate and urgent problems with which it is their fate to deal, there should yet be a reservoir of synthesized and clarified knowledge on which they can draw. The technique which brings governments in contact with scientific knowledge in particular, though greatly improved of late, is still imperfect. In any case the politician is perforce concerned with the present rather than the future. I have recently read Bacon's "New Atlantis" afresh and have been thinking about his Solomon's House. We know that the rules for the functioning of that House were mistaken because the philosopher drew them up when in the mood of a Lord Chancellor; but in so far as the philosopher visualized therein an organization of the best intellects bent on gathering knowledge for future practical services, his idea was a great one. When civilization is in danger and society in transition might there not be a House recruited from the best intellects in the country with functions similar (*mutatis mutandis*) to those of Bacon's fancy? A House devoid of politics, concerned rather with synthesizing existing knowledge, with a sustained appraisement of the progress of knowledge, and continuous concern with its bearing upon social readjustments. It is not to be pictured as composed of scientific authorities alone. It would be rather an intellectual exchange where thought would go ahead of immediate problems. I believe, perhaps foolishly, that given time I might convince you that the functions of such a House, in such days as ours, might well be real. Here I must leave them to your fancy, well aware that in the minds of many I may by this bare suggestion lose all reputation as a realist!

I will now hasten to my final words. Most of us have had a tendency in the past to fear the gift of leisure to the majority. To believe that it may be a great social benefit requires some mental adjustment, and a belief in the educability of the average man or woman.

But if the political aspirations of the nations should grow sane, and the artificial economic problems of the world be solved, the combined and assured gifts of health, plenty and leisure may prove to be the final justification of applied science. In a community advantaged by these each individual will be free to develop his own innate powers, and, becoming more of an individual, will be less moved by those herd instincts which are always the major danger to the world.

You may feel that throughout this address I have dwelt exclusively on the material benefits of science to the neglect of its cultural value. I would like to correct this in a single closing sentence. I believe that for those who cultivate it in a right and humble spirit, science is one of the humanities—no less.

SCIENTIFIC EVENTS

SURVEY OF THE SHRIMP INDUSTRY BY THE BUREAU OF FISHERIES

PLANS have been completed by the Bureau of Fisheries to conduct an economic survey of the shrimp fishery of the southern states to dovetail with the biological survey which has been in progress for several months.

Frank T. Bell, commissioner of fisheries, in announcing the survey, pointed out that the shrimp fishery in 1929 ranked fifth in order of value to fishermen and ninth in volume among all fisheries of the United States. In that year, the shrimp fishery produced 113,000,000 pounds valued at $4,575,000 to the fishermen. Since then the value and volume have decreased slightly.

The purpose of the economic survey, which will be made by F. F. Johnson, of the bureau, is to supply shrimp fishermen with information on production and marketing conditions, as well as general information intended to facilitate the more orderly pursuit of the fishery.

The biological study has produced more tangible results in the past year than all previous studies of this type. Among other things, it has been determined that the life span of the shrimp is but one year. This fact establishes the necessity of "timing" the harvest so that the shrimp may be taken at a time when they have attained the best size from a market standpoint, and that allowances also may be made for spawning.