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THE ANIMAL CELL IN THE LIGHT OF RECENT WORK.

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With the discovery of the centrosome, microscopical work on the animal cell apparently reached its culmination. It was predicted that further study would yield little more than the details of larger facts already known. The last few years have marked the addition of just such details in even greater measure than was imagined; but it is also true that altogether unexpected contributions have been made from work along other than classic microscopical lines. Especially to be mentioned are: (1) the application to the cell of the data and the methods of physical chemistry; and (2) the extension of experimental biology to the field of the animal cell. The solid facts derived from these newer studies are already numerous, with every indication of vigorous growth occurring daily. But before the full value of these new facts can be appreciated, they must be coördinated with the older conceptions. Probably at no time following the reorganization of the cell-theory by Max Schultze in 1861 has there been more urgent need for a critical survey of results than the present moment. The writer does not claim completeness for the paper here presented; the space prescribed is all too limited for even a complete summary. Rather, the attempt has been made briefly to outline certain facts which have an important bearing on some of the modern problems of the animal cell.

I. THE MINUTE STRUCTURE OF PROTOPLASM.

Any conception of cell-life must involve the microscopical architecture of living substance as such. The oldest view, and the one still widely current, presents protoplasm as everywhere having the structure of a reticulum holding more fluid matter in its meshes. The accuracy of this conception could not be tested before optical apparatus had been somewhat improved, and until the effects of laboratory reagents upon the microscopical appearance of protoplasm had been thoroughly grasped.

Hardy took a step in the right direction through his fine studies of the structure of colloidal solutions and the effects of reagents upon them. Fischer, in a series of carefully planned researches, applied our common fixing and staining agents, in accordance with biological usage, to proteids, proteoses, and peptones. Such work demonstrated that our laboratory methods, when blindly followed and implicitly trusted, are productive of altogether misleading pictures in stained and mounted preparations.

Logically, the next contribution (although historically antedating the studies just noted) was made by Bütschli from his investigations of artificial foams and emulsions, and in the application to protoplasm of the results so obtained. It was thus made clear that a series of *alveoli* would optically present the *reticulum* described by Heitzmann, Leydig, Carnoy, Schäfer, and Watasé; or the *fibrillae* of Flemming and Schneider, when protoplasmic currents and optical conditions are favorable; or the *granules* of Altmann, when nodes are emphasized, or when the reagents employed are productive of clumped artifacts. It was certainly a marked advance to have it shown that the earlier attempts to find exact uniformity of ultimate protoplasmic structure amid all diversities of living conditions were but partial expressions of one truth.

Building on the foundation laid by Bütschli, the Andrews in "The Living Substance" and later papers have brought to completion a conception of protoplasm which may well endure. It is a weighty discovery that the walls of Bütschli's alveoli are themselves vesicular, the vesicles forming an infinitely graded series down to the extreme range of microscopic vision; and, further, that there is the most ready interchangeability from one size of vesicle to another. All structural features of the cell, when optically dissected, are seen to be due to vesicles in a matrix. Protoplasm thus embraces two series of structures: (1) the *continuous substance*—the matrix, the active part, everywhere continuous throughout the cell, optically uniform; and (2) the *inclusions*, held by the matrix of continuous substance, infinitely heterogeneous as to size and constitution—solid, liquid, or semi-liquid—arranged in a great variety of ways. The microscopical appearance of any protoplasm is determined by the character and arrangement of its inclusions. Differences of structure and function are due to differences in the inclusions. Vital phenomena may be conceived to result from the interaction between the continuous substance—everywhere uniform, and the inclusions—everywhere varied.

This conception of protoplasm as a microscopical substance illumines, as with a flood of light, the phenomena of cell-life. We are thereby prepared for an understanding of the entrance of matter into the cell; of the translation of matter from one point in the cell to another; to grasp the basis of the chemical reactions which occur in the cell; to realize how the results of irritation spread so readily; and to find a physical basis for the unity of the organism.

II. THE CHEMISTRY OF PROTOPLASM.

It certainly is significant that the elements composing living matter are not scattered at random through the natural system, but that they comprise a fairly well-defined group, characterized by low atomic weights. The extreme lability of protoplasm as a substance is doubtless the direct outcome of the instability of the compounds which these very elements tend to assume.

Not less significant is the fact that protoplasm is a watery substance, holding certain salts in small quantities.

It is worthy of special emphasis that the chemical reactions of the cell invariably occur in a liquid which is really a dilute solution of electrolytes. Free ions certainly have to be reckoned with in the phenomena of cell-life.

Among the organic constituents of the animal cell, the proteids must be accorded first place. These exist in several degrees of complexity. The simple globulins and albumins are found in both cytoplasm and nucleus; these represent the lowest step in the process of assimilation. Combined proteids hold a larger place in cell-life, particularly the members of the nuclein series. Chromatin is a nuclein rich in nucleic acid, relatively poor in proteid. Its richness in acid is expressed by the deep stain which it assumes with basic dyes. The nucleolus has a lower percentage of nucleic acid, a higher percentage of proteid. Nucleo-proteids are characteristic of the cytoplasm, a maximum of proteid having combined with the nucleic acid. It is highly suggestive that the successive additions of proteid to the molecular constitution of the nucleo-proteids of the cell take place from the chromatin outward into the cytoplasm.

Lecithin and cholesterin are components of both cytoplasm and nucleus. The place of lecithin may be next to that of the proteids in order of importance. Its presence in quantity in nervous tissue is the basis for the ready absorption and specific action of anæsthetics.

The carbohydrates and fats of the animal cell are marked off sharply from the foregoing classes of constituents by the fact that they are limited to inclusions in the cytoplasm.

A proper interpretation of the conditions for cell-life requires us to hark back to the fundamental work of Graham on colloids. Because of the high percentage of proteids in the cell, the bulk of protoplasm consists of colloidal matter in water. Following the nomenclature of Graham, protoplasm is a sol; and since the colloidal particles are held suspended in water, protoplasm is really a hydrosol. Protoplasm exhibits the properties of colloidal solutions generally, passing readily into the gel condition, a hydrogel. Protoplasm, moreover, presents the most complete reversibility of the process, the sol passing into the gel and the gel back into the sol again, so long as conditions for vital phenomena persist. The importance of this fact in the life of the cell has not as yet been fully grasped by biologists generally.

No less fundamental is the recent brilliant work of Hardy on the conditions which are productive of gelation in colloidal solutions. A sol of proteid was used, and it was made clear that the gel state is produced by the addition of electrolytes but not by non-electrolytes, unless these act chemically; and that the gelation from electrolytes is due to the electric charges carried by the ions was demonstrated by the identical results following the use of an electric current from a battery. Moreover, the signs of the electric charges carried by the ions,—positive or negative,—determine the movements of the colloidal particles, keeping them in suspension as a sol, or causing them to fall into the gel condition. For example, a sol having its colloidal particles negatively charged will pass into the gel state upon the addition of positive ions, or the introduction of the positive electrode of a battery.

These remarkable results indicate the importance of ions in the life of the cell, and they also serve to clarify many phenomena hitherto quite obscure. The rapid changes in the consistence of protoplasm have long been known from observation, but they have never been explained; these fascinating alternations of more rigid and more fluid conditions are now seen to rest upon the state of the colloids of the cell, the controlling factor being the ions set free as the result of chemical reactions. Peculiarities in the toxic effects upon protoplasm of certain substances have long been a puzzle; but such effects are now recognized as due to the electric charges carried by the ions rather than to the chemical nature of any particular substance employed.

III. THE NUTRITION OF THE CELL.

The ingestion of matter, standing as the alpha of cell-life, may well command attention. It is somewhat unfortunate that laboratory studies of the Protozoa exhibit so prominently the entrance of solid matter into the cell, for this condition is really quite rare in the animal series. Matter is so universally floated into the cell in water that the problem of its entrance is, in fact, the problem of the absorption of a solution. The field is a promising one for further research, but sufficient has already been done to show that the principles of osmotic pressure find application here. The architecture of protoplasm and its chemistry are such that conditions for a greater or less amount of osmotic pressure are always present. Now, since food reaches the cell in solution, van't Hoff's work on osmotic pressure shows that its absorption is not a peculiarly mysterious phenomenon, but that the vital results are in harmony with the principle of the conservation of energy. Even the choice of matter, so universally exercised by the cell, rests on relative osmotic pressures, depending upon the peculiar constitution and chemical reactions of the protoplasm in each instance.

The transforming effects upon matter of enzymes hold so necessary a place in animal life that attention has long been directed to this field. Here again, the understanding of the principle involved places the biologist in the debt of the physical chemist. The study of colloidal solutions or sols of metals has been illuminating to a remarkable degree. Platinum, gold, silver, iridium,—when brought to an extremely minute state of subdivision, by methods which need not here be described, behave as catalyzers to such an extent that these sols have been called "inorganic models of the enzymes." An enzyme is, of course, immensely complex in composition as compared with the inorganic model, being the result of cellular activity—a nucleoproteid; but its minute subdivision is certainly at least as important as its chemistry.

In the metabolism of matter, the proteids assuredly have the pivotal place. The assimilation of proteid involves the reconstruction of the molecule,—"aggregate"—upon an altogether different plan, whereby a state of the greatest instability is given. The condition for this instability is the intramolecular introduction of oxygen.

The members of the nuclein series begin with nucleic acid, a compound of phosphoric acid and the nuclein bases adenin, hypoxanthin, guanin, and xanthin. Of these bases, adenin is fundamental, because its molecule contains no oxygen, and the other bases are derivable from it. Adenin may be looked upon as of the utmost importance in synthetic processes, since under conditions of reduction the oxygen-free adenin may be transformed into a new body with avidity for oxygen; and this, in turn, may be again transformed by the addition of new "aggregates." Hence adenin may be the starting-point in the synthesis of nucleins of successive grades,—the nuclein of chromatin, that of the nucleolus, and the nucleo-proteids of the cytoplasm. That nucleins do arise from the synthesis of simple proteids and phosphates has been shown by Miescher in the salmon, where the muscles are converted into the material of the ova during the ascent of the fish to the breeding-grounds.

The study of the nuclein series points to the nucleus as the center for the initial syntheses. The many instances of the reciprocal relations between nucleus and cytoplasm here receive almost startling explanation. The work of Mathews on the pancreas-cell demonstrated the origin from the chromatin of fibrils of nucleo-proteid which are spun out into the cytoplasm. We appear to have here, before our very eyes, the basis of the "intracellular pangenesis" of de Vries. Place beside this result the work of Loeb on the seat of oxidation in the cell, and it is clear that the nucleus holds a controlling place in cell-life because synthetic steps are initiated there. We are thus enabled to appreciate the significance of the position assumed by the nucleus in the growing cell; the changes in the microscopical appearance of the nucleus during periods of cell activity; the dependence of the cytoplasm upon the nucleus in regeneration experiments; and the real value of the nucleus in the field of heredity. This does not mean that the nucleus is more important than the cytoplasm in cell-life, for the two stand in a mutual relationship necessary to each other.

The importance of lecithin in metabolism has been shown by the feeding experiments of Hatai. This substance evidently represents a distinct step in the process of assimilation in the animal cell.

The absence of carbohydrates and fats from the nucleus signifies that these substances are transformed and split up entirely in the cytoplasm. The place of proteid in metabolism, then, may be regarded as primary; that of the carbohydrates and fats as secondary.

In the field of excretion there is less of experimental evidence to serve as the basis for an adequate conception, and it is probable that quite diverse mechanisms must be recognized. The work of Dreser is very suggestive, however, showing that excretion from the cells of the uriniferious tubules may be calculated on the basis of osmotic pressure.

IV. THE TRANSFORMATION OF ENERGY IN THE CELL.

Animal biology may begin to claim recognition as an exact science. It has passed beyond the merely descriptive stage and has demonstrated beyond question that the principle of the conservation of energy really holds in the activity of the animal cell. Potential energy is introduced into the cell from without along with the matter of food and oxygen. Foods are substances whose elements have a relatively feeble affinity for each other as compared with the affinity which each element has for oxygen. The accurate measurement of the potential energy of foods is necessarily recent; the determination of the kinetic energy of the organism, even more so. But the difficulties have been overcome by the intelligent co-operation of many workers:—the efforts of Atwater and his collaborators should be especially mentioned. We stand today on a secure foundation of fact, not inference, that chemical energy is the only source for the energy appearing in the animal cell in its several kinetic forms—heat, light, mechanical work, electricity.

The production of heat and light in the animal cell involves transformations most readily understood. Just as oxidation in a physical system other than the living transforms the potential energy of organized matter into heat, so, in the animal cell, heat is the direct outcome of the chemical transformations of dissimilation. Since light and heat are but different phases of the same radiant energy, so the basis of light-production in the cell is the same as for heat-production. Experimentally, the oxidation of fatty granules in the presence of an alkaline medium yields light. Special phosphorescent organs are cell-groups where such fatty particles, resulting from metabolism, are burned in an abundant supply of oxygen. It is possible that light is a more widespread accompaniment of cell-life than is usually supposed.

The transformation of chemical energy into the mechanical energy of movement is slightly less direct, involving surface tension. Experimental work with oil-drops shows that amœboid movement is the simplest condition and should be taken as the starting-point. An amœboid cell has its surface unspecialized, permitting freedom of movement. With surface tension equal at all points, the form of such a cell must be that of a sphere. It is evident that a local alteration of surface tension must result in a corresponding change of form at the point where alteration occurs. Reduction of surface tension will be expressed by the formation of a pseudopodium; increase of surface tension by its retraction. Now, the chemical changes occurring in living matter provide the conditions for the alteration of surface tension. The introduction of oxygen increases molecular instability, leading to the reduction of surface tension and the protrusion of pseudopodia; reconstruction of the molecule must, conversely, increase surface tension, causing the retraction of pseudopodia. Thus the phenomena of movement result from local differences of chemical action. Recent work has made it clear that ciliary movement, and the still more specialized contraction of a muscle-cell, are derivable from the simple conditions just sketched.

Electricity is an invariable accompaniment of vital processes, whether in the contraction of a muscle-cell, the secretion of a gland-cell, the changes of nervous matter, or the truly striking discharge of a specialized electric organ. Electrolytic dissociation is the basis for the development of animal electricity in all its fascinating guises, chemical reactions continually altering the relations of ions. Differences of potential are due to the fact that not all parts of a cell or group of cells are active at the same time. It has long been known that protoplasm acquires an acid reaction as the result of its activity. In terms of physical chemistry, this fact means that positive hydrogen ions are set free. Such ions migrate from the active into the passive protoplasm more rapidly than do the anions, hence the regions where vital processes are taking place remain negatively charged, as all our experimental work has long shown.

V. THE IRRITABILITY OF PROTOPLASM.

From the standpoint of cell-chemistry, the irritability of living matter is nothing more than the modifications induced by external conditions in the course of the transformation of matter and energy in the cell. A modern high-explosive is just as truly irritable as is protoplasm, having the equilibrium of its matter and energy disturbed by the impact of kinetic energy from without. In the case of living matter, the external energies productive of such disturbances are called "stimuli," a somewhat unfortunate term. Obviously, the effect of stimulation,—the introduction of kinetic energy from without,—is to divert the course of chemical reaction in the cell, causing a corresponding change in the kinetic energy liberated,—movement, heat, light, electricity. The change in the electrical condition necessarily influences the behavior of the colloidal particles of protoplasm. Mathews would find the basis of conductivity in a wave of gelation in the colloids of irritable tissue.

"Taxis" or "tropism" in its several forms is today seen to result from the unequal stimulation of a cell at its opposite poles. The minuteness of the possible differences between the strength of stimuli at the two extremities of a cell is best seen in chemotaxis. But however small this difference, if it be sufficient to affect the transformation of energy at the pole proximal to the stimulus, unilateral movement must result. Hence the wonderfully fascinating directive effects of external agencies upon the lower organisms rest upon local differences of chemical reaction in the cell.

Work on the motile Infusoria has indicated in a very striking way the nature of a reflex. Whatever the form of stimulus,—mechanical, thermal, chemical, electrical,—the same reflex is exhibited. This reflex is itself invariable, embracing an arrest of the forward progression, a swimming backward, a turning toward a structurally defined side, then a swimming forward. Such a reflex is entirely effective under the usual conditions for the life of the animal, because the anterior extremity first comes in contact with sources of danger, and the series of movements leads to the danger being avoided.

An insight into adaptation to environment has been given by the fine work of Jennings upon fixed Infusoria, particularly Stentor. Here it was shown that protoplasm has results wrought into it from the previous experiences to which the organism has been subjected. The behavior of Stentor during the course of repeated stimulation soon begins to show traces of after-effects from the stimuli which have just preceded. Such adaptation to conditions must have its basis sought in alterations produced in the architecture and chemistry of protoplasm under the impact of energy from without, the modification of structure persisting for a greater or less time. The field is certainly a fruitful one for further and more refined investigation.

Nervous tissue is rapidly developing an extensive and highly ramified literature of its own. The tendency is current, on the part of at least a few neurologists, to neglect the boundaries of the nerve-cell altogether, placing emphasis, instead, on the continuity of neuro-fibrils throughout the entire nervous system. It may safely be said, however, that a healthy condition of the subject will require proper recognition of cell-values.

VI. THE REPRODUCTION OF THE CELL.

The phenomena of development are recorded in a literature which has become truly voluminous, but only during very recent years has the work passed beyond the purely descriptive stage. Experimental embryology has made very rapid progress, however, and the achievements already to its credit are so noteworthy as to give promise of a brilliant future.

Fertilization is now definable as a distinctly twofold process. The factor first recognized, the transfer of chromatin, has long been known in the most minute detail. The other factor, but recently distinguished as such, is the stimulus to development which results from the entrance of the spermatozoön. Oögenesis leaves the ovum in what may be called the first critical stage of the organism, in which the living material has reached a condition of such stability that death soon occurs unless the stimulus of fertilization be given. This stimulus is conveyed by the spermatozoön normally; but the experimental studies of Loeb and others have made it clear that a variety of stimuli may be productive of artificial parthenogenesis. A change of osmotic pressure, even mechanical shock, will induce development from this critical condition. Eggs which are normally parthenogenetic find the stimulus proper to their development amid natural surroundings, without the intervention of fertilization at all.

A few lines of work are now to be touched very lightly, and the bare mention of others must be omitted altogether. In the field of mitosis, the models of Heidenhain have at least furthered our understanding of the mechanism involved. Experimental methods have shown that astral rays and spindle fibres are rows of vesicles spun in the cytoplasm, expressive of currents or lines of chemical action. That much-discussed thing, the centrosome, is no longer considered a definite morphological body, but rather a center for a special transformation of energy, to be induced at points in the cell other than the normal ones under certain conditions. The division of the cytoplasm certainly involves a localized change of surface tension; and the forms assumed by the individual blastomeres during cleavage involve surface tension as one of the factors.

The studies of Wilson, Driesch, Morgan, Lillie, Conklin, Boveri, Crampton, and others on localization in the egg are among the most important of modern times. Begun for the purpose of putting to experimental test the hypotheses of Roux and Weismann, this line of work has long since outgrown its original impetus, and has illumined some of the deepest problems of the cell. Differentiation, as these studies have shown, is a feature of the cytoplasm. It is in the nature of a progressive change, whereby the cytoplasm of the egg becomes ever more and more localized into definitive regions, it may be very early in the history of development. Cleavage is merely a means of dividing up this material into cell-units; the exact process is relatively unimportant, differentiation lying far behind cell-boundaries. Localization, while thus cytoplasmic in character, is really determined from the nucleus, and is carried out in the cytoplasm through specific metabolisms which are set up. There is more than a simple parallel between the course of determination and the course of synthesis in the cell. Chromatin is the center for the initial steps of both, and the nucleus holds a definite place in development because of the place it holds in metabolism.

The energy of growth is indeed a conspicuous feature of the developing cell. To say that growth occurs because of the introduction of material from without is a mere truism; the forcible expansion of the cell is indicative of an energy which lies behind the entrance of matter. The energy of growth is but a special instance of osmotic pressure, the rhythms of which are expressive of the metabolisms in progress.

The life-history of the metazoan cell involves many successive divisions, the earlier mitoses occurring rapidly, the later ones more and more slowly. There finally comes a time when the cell reaches its second critical stage, a condition of stability whose end is death. The first critical stage has been averted in the history of each organism through fertilization; but in the second critical stage, such a stimulus is clearly impossible for the metazoan cell. The work of Calkins on Paramœcium, however, has demonstrated that an artificial substitute for conjugation may be found for the infusorian cell,—meat broth, extract of brain or pancreas,—whereby the second critical stage is passed. The bearing of this result on the metazoan cell is obvious. Probably certain tumors represent cells which, having approached the point of stability, have been stimulated to renewed activity by the presence of unusual ions.

VII. CONCLUSION.

Students of the animal cell may well look upon the results of modern work with no small degree of satisfaction. A large body of solid knowledge concerning vital processes has grown up during recent years, very different from the vague and even mysterious assumptions which lurked here but a short time ago. One conclusion to be drawn from the facts established is the marked degree to which physical principles have been extended into the domain of the vital. Some workers, as Le Dantec, swing the pendulum to the farthest limit in this direction, seeing nothing but *mechanism* in the life of a cell. Others there are, who, unable fully to appreciate the physical basis of cell-life, insist on pushing the pendulum to the opposite extreme, calling this position *vitalism;* a position "where", to quote Kant, "reason can repose on the pillow of obscure qualities."

The question properly may be asked, how rapidly is the investigation of the cell nearing its goal. Such an end is as yet far distant; du Bois-Reymond declared that it could never be attained at all. To-day, we know certain phases of cell-life fairly well, but the obstacles in the way of further progress are more serious than those already surmounted. However, the biology of the cell has by no means reached a dead-point; we have but just begun to make full use of the data afforded by sister sciences; the experimental method has yet rich treasures to yield. We assuredly are justified in concluding that one field after another will continue to be reclaimed from obscurity in the future just as in the past, and we reasonably may expect a working conception of cell-life ultimately to emerge from modern investigation.

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