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CONTENTS

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SUGGESTIONS FOR PHYSICAL INVESTIGATIONS BEARING UPON FUNDAMENTAL PROBLEMS OF PHYSIOLOGY AND MEDICINE[1]

Since diseased conditions imply deranged cell-processes—leading to failure of local functioning or to defective coordination between the activities of different parts of the organism—it is clear that the problem of preventing and rectifying such derangements in man (the problem of medicine) resolves itself ultimately into the means by which cell-processes can be restored to the normal after disturbance. A scientific (as distinguished from an empirical) knowledge of how to restore normal conditions must be based on an exact knowledge of the conditions determining normal protoplasmic activity, and this knowledge presupposes a fuller insight into the fundamental physico-chemical constitution of protoplasm, since it is only through an understanding of the properties of the essential living substance that we can hope to understand how the living system acts under different conditions.

The fundamental questions are thus: what kind of a system, in the physico-chemical sense, is living protoplasm? and what are the conditions of equilibrium, *i. e.*, of normal self-maintenance, of such a system?

As a physico-chemical system protoplasm is peculiar in various respects, of which perhaps the chief are:

1. The self-maintenance of the system through its own continued chemical activity; *i. e.*, the preservation of the normal equilibrium—or continued life—depends upon the active continuance of the chemical processes

[1] Contribution to the discussion at the Conference on Biophysics held by the National Research Council, Division of Medical Sciences, at Washington, February 21, 1920.

of the protoplasmic system, *i. e.,* upon metabolism.

2. This metabolism involves a continual construction of complex specific compounds—typically compounds of high chemical potential—to replace those disintegrated (as a result or oxidation or otherwise) in the energy-yielding or otherwise destructive processes of protoplasm.

3. The rate and in part the character of both the energy-yielding and the constructive metabolism are readily influenced by changes in the external conditions: *i. e.,* protoplasm is a characteristically *irritable* system—one of unstable equilibrium.

4. The ratio of constructive to destructive metabolism may vary widely under different conditions; excess of construction over destruction involves growth; equality of the two is equilibrium, implying a stationary condition as regards size and properties; while excess of destruction leads to regression, as in starvation. Obviously regression, if sufficient, must impair functional capacity and eventually lead to death.

5. The power of *growth* is thus inherent or potential in all forms of protoplasm during life. Those pathological problems which relate to excessive or otherwise abnormal growth or proliferation (*e. g.,* the case of tumors) thus require for their scientific solution a knowledge of the physico-chemical conditions of normal growth.

It is evident, since growth is an inherent property of the living system—*i. e.,* since the continuance of the living state depends on this power of specific construction—that the problems just cited relate themselves directly to the general group of problems having reference to the essential physico-chemical constitution of protoplasm. The protoplasmic system is primarily a growing or synthesizing system, at the same time as it is a system which continually yields material and energy to the surroundings through the chemical breakdown of certain components. The chief aim of general physiology is to understand the type of physical and chemical constitution that makes possible chemical activities of this general kind.

Experiment shows that destroying the structure of protoplasm, by mechanical or other means, destroys most (though not all) of its chemical activity (including the latter's susceptibility to electrical influence), and in particular its power of specific synthesis or growth. Hence this power must depend on the special structure of the system. The chemical reactions constituting metabolism take place within a field or substratum having a special type of structure (*i. e.,* arrangement of phases); and the nature and rate of the metabolic reactions are controlled by the structural conditions present. These structural conditions are themselves produced by the growth of the system itself, or of another system having similar properties.

It must be recognized that the problem of the fundamental constitution of living protoplasm underlies all of the problems of biology—including ultimately those of medicine, as a branch of applied biology. It is therefore all-important from the practical as well as from the purely scientific standpoint that this problem should be the subject of continual and active study and investigation.

Physical Processes of Fundamental Importance in Protoplasmic Activities.—The research of the past fifteen years has made especially clear the importance of surface-processes in the activity of living matter. The behavior and properties of colloids (the substances composing most of the solid material of protoplasm) are largely determined by surface conditions (adsorption, variations of phase-boundary potentials, interfacial tensions). Electrical stimulation depends upon sudden changes in the electrical polarization of the semi-permeable surfaces of the irritable cell. Protoplasmic movement (muscular contraction, etc.) is almost certainly due in most cases to the changing surface-tension of the structural elements composing the contractile fibrils. Growth processes show various significant resemblances to structure-forming processes occurring under the influence of local electrolysis at metallic surfaces in contact with electrolyte solutions (formation of precipitation-tubules of zinc or iron ferricyanide, rust-patterns, etc.). Transmission-effects in protoplasmic systems (*i. e.*, in nerve, etc.) may be closely paralleled by processes of chemical transmission or distance-action in film-covered metallic systems, like passive iron in nitric acid or mercury in hydrogen peroxide. Many cell-processes are associated with changes in the osmotic properties or permeability of the protoplasmic surface-films or plasma-membranes. The high development of surface layers or membranes is in fact a long-recognized structural peculiarity of living matter. The prevalence of the cellular type of organization is in itself evidence of the fundamental importance of this condition.

These general facts indicate strongly that for the purpose of gaining further insight into the physico-chemical constitution of living matter a more thorough and detailed study (1) of the general properties of surfaces (their structure, tension, electrical properties, etc.), (2) of the layers of material formed at surfaces (surface-films, etc.), and (3) of phenomena dependent on surface conditions (adsorption, catalytic effects, flocking and peptization of colloids, etc.), is all-essential. Probably the purely physical or chemical investigation of these problems will best be undertaken by students trained in the methods of physics and physical chemistry. Data or principles so obtained can then be applied to biological or medical problems by those specially qualified to deal with such problems.

There is much evidence that living protoplasm is essentially *emulsion-like* in its fundamental physical constitution; and it is known that the properties of emulsions are largely determined by the presence of interfacial films and by the electrical and other conditions resident at the phase-boundaries. The general physical and chemical conditions affecting the stability and properties of emulsion-systems are thus in large part identical with those affecting the stability and properties of living protoplasm. As is well known, emulsions are mixtures of two (or more) mutually insoluble liquids, of which one is in a state of fine division and dispersed throughout the other; for stability a third substance (*e. g.*, soap), forming a surface-film between the two phases, is usually required. Recent work has shown that the properties of oil-water emulsions may be made to vary in a remarkable manner by varying the salt-content of the system, and that these changes depend upon the solubilities of the soaps formed and upon their surface-activity. Many surprisingly close parallels between the effects of different combinations of salts on emulsion-systems and on living protoplasmic systems have been demonstrated. It is well known that the presence of inorganic salts in definite proportions is essential to the normal activity of most living cells. Such results, therefore, indicate the importance of initiating and extending researches which will have as their object the determination of the relation between the soluble substances (both electrolytes and non-electrolytes) present in emulsion-systems and the general physical properties and behavior of such systems. Light may thus be thrown upon the general properties of protoplasm (mechanical properties, structure, permeability, electrical properties), in so far as these properties are determined by the emulsion-like constitution of the system.

This emulsion-structure, however, furnishes only the field or substratum in which the essential chemical reactions (or metabolism) of the living protoplasm proceed. The special nature of these chemical processes determines the special properties and behavior of the protoplasmic system. Hence the relation of the film-pervaded or emulsion-like structure of protoplasm to the special type of chemical activity exhibited by the living system should be thoroughly studied and investigated. There are many indications that the extraordinary chemical capabilities of living matter are dependent upon the extent of its surface development: *i. e.*, that the influence of protoplasm in inducing chemical reactions not found elsewhere is essentially the result of the special predominance of surface influences of a peculiar kind. And since the sensitivity of living matter to the electric current is one of its most characteristic peculiarities, it appears probable that the chemical reactions in protoplasm are largely controlled by variations in the electrical potential-differences present at the various protoplasmic phase-boundaries (the surfaces of membranes, fibrils, etc.). At present our knowledge of chemical processes occurring under electrical control is almost entirely confined to those observed at the surfaces of metallic electrodes in contact with electrolyte solutions. These are the well-known phenomena of electrolysis. Knowledge of such processes should be extended to include the case of electrolysis at other interfaces, *e. g.*, between an oil phase and a water phase. The technical difficulty here appears to be largely one of conducting the current through the non-aqueous phase. But since many of the chemical reactions in protoplasm are demonstrably under electrical control, it is clear that metallic surfaces (*i. e.*, metallic electrodes) are not necessary to the production of chemical effects by the electric current. Apparently in the living cell surfaces of other composition play the same part. There seems to be here a field of investigation which should throw much light upon the conditions of the chemical processes in protoplasm. The phenomena of polar stimulation, polar disintegration and similar effects in physiology are an obvious counterpart of the polar differences between the chemical effects of anode and cathode in electrolysis. Undoubtedly the same fundamental basis exists for the polarity in the chemical effects of the electric current in the living and in the non-living systems. The effects produced by passing currents through appropriately constituted emulsion-systems containing readily alterable (*e. g.*, oxidizable) chemical compounds might well be investigated to advantage in relation to this problem. Closely related also would be a study of the surface-films formed at the interfaces between pairs of fluids, or between fluids and solids, and the effects of electrical and other conditions upon such films.

Progress in these and related departments of physical research would undoubtedly be of great service to general physiology at the present stage of its development. Many fundamental physiological processes—growth, cell-division, muscular contraction, response to stimulation, transmission of stimuli, chemical control of metabolism, etc.—must remain imperfectly intelligible without the extension of exact knowledge in these fields. The possibilities of the control of vital processes, including the control of diseased conditions, would certainly be greatly enlarged with a more fully developed general physiology. The problems suggested above have many aspects of purely physical and chemical interest, apart from their physiological bearing; and it is to be hoped that properly equipped investigators may be found to engage in their study.

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THE LONGNECK SAUROPOD BAROSAURUS[1]

In 1889 Professor O. C. Marsh secured from the shales overlying the sandstones following the marine Jura, near Piedmont on the eastern "Rim" of the Black Hills, various fragmentary caudals of a huge sauropod. In these he recognized a new type which he called *Barosaurus lentus*. He had been kindly advised of the occurrence, and was accompanied by the noted collector J. B. Hatcher, but attempted no adequate excavation.

Nine years later, in the midwinter of 1898, after a friendly letter from Professor Marsh, I visited him at New Haven and discussed the subject of field work in the west for the succeeding summer. Knowing that after Hatcher left Yale several years earlier the field work on the Dinosauria had suffered, I

[1] 1890. O. C. Marsh, *Barosaurus lentus* gen. et spec. nov. in "Description of New Dinosaurian Reptiles," *Amer. Jour. Sci.*, January, page 86, Figs. 1 and 2. 1919. R. S. Lull, "The Sauropod *Dinosaur Barosaurus* Marsh—Redescription of the Type Specimens in the Peabody Museum, Yale University," *Memoirs of the Connecticut Academy of Arts and Sciences*, Vol. VI., pp. 1–42, with figures in text and 7 plates.