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# "FATHERS" AND "SONS" OF THEORIES IN CELL PHYSIOLOGY: THE MEMBRANE THEORY

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**Abstract** - The last 50 years in the history of life sciences are remarkable for a new important feature that looks as a great threat for their future. A profound specialization dominating in quickly developing fields of science causes a crisis of the scientific method. The essence of the method is a unity of two elements, the experimental data and the theory that explains them. To us, "fathers" of science, classically, were the creators of new ideas and theories. They were the true experts of their own theories. It is only they who have the right to say: "I am the theory". In other words, they were carriers of theories, of the theoretical knowledge. The fathers provided the necessary logical integrity to their theories, since theories in biology have still to be based on strict mathematical proofs. It is not true for sons. As a result of massive specialization, modern experts operate in very confined close spaces. They formulate particular rules far from the level of theory. The main theories of science are known to them only at the textbook level. Nowadays, nobody can say: "I am the theory". With whom, then is it possible to discuss today on a broader theoretical level? How can a classical theory - for example, the membrane one - be changed or even disproved under these conditions? How can the "sons" with their narrow education catch sight of membrane theory defects? As a result, "global" theories have few critics and control. Due to specialization, we have lost the ability to work at the experimental level of biology within the correct or appropriate theoretical context. The scientific method in its classic form is now being rapidly eroded. A good case can be made for "Membrane Theory", to which we will largely refer throughout this article.

**Key words**: Membrane theory, cell physiology, scientific method, specialization

## INTRODUCTION

At present, it is commonly accepted that the most characteristic feature of the modern science is its marked specialization. Even researchers studying similar cellular structures – for instance, channels – live now in parallel worlds: those who study Na-channels do not see too much sense in communicating with those who study Ca-channels, and even less with those who study channels for organic molecules. Of course, expanding specialization is not merely a sensation or individual observations. We see everywhere objective evidence of degradation of sciences into individual "earldoms" whose autonomous status is constantly being enhanced. The most evident proof in favor of this is a rise in the number of co-authors on publication, reaching in some cases up to several hundred names. Also the number of specialized journals and conferences is steadily increasing. The mean length of formulations of the essence of discoveries, for which Nobel Prizes are awarded, increases, while the number of "discoveries" decreases and their significance can only be correctly evaluated by an increasingly narrow circle of specialists. The decrease of significance of investigations on the background of a steady rise of the number of publications means that expenditure on science increases, while their actual yield decreases. But whereas economic consequences of the specialization are widely discussed, the intellectual problems that beset modern science still escape proper attention.

The danger has descended through "Scientific Method" itself. Theories of a general biological character were accepted many decades ago, and nowadays, due to the specialization, there are no scientists who master these theories so well as those who could be rightfully considered their bearers. As a result, the profound generalizations of the past seem to be beyond the natural process of renovation, and indeed beyond criticism. If competing theories appear under these conditions, their significance and advantages over classical knowledge will not be properly evaluated - fantastic and worrying as this might seem. There has appeared or can appear the situation where scientists mastering the most modern methods of

investigations at the molecular level are guided in their work by obsolete or even erroneous concepts of the general character that they inherited from the classicism epoch. *The theories of the past, instead of being always under scrutiny, have turned into the dogmas incompatible with the spirit of the scientific method.* The extra layers of present day specialization are a menace, which may lead to the loss of the integrity of scientific knowledge.

## SCIENTIFIC METHOD IN AN EPOCH OF SPECIALIZATION

In the opinion of Popper (10), the structure of the scientific method seems to be as follows: i) identification of problem (for instance, failure of a previous theory); ii) proposal of a new solution (i.e. of a new theory); iii) deduction of verifiable conclusion, predictions from this theory; iv) choice of the most suitable theory among the competing ones. Let us consider the effect of the process of progressing specialization in science on functioning of the scientific method as the main instrument of scientific investigation.

The overwhelmed number of authors writing about scientific method find the most illustrative examples of its application in history of science – e.g. failure of Ptolemaeus' theory, establishment of Copernicus' system, the appearance of Newton's classical physics, Einstein, etc. But let us imagine for a while a fantastic case: in the XIX century, after the 300-year long development of Newton's mechanics, the degree of specialization in physics reached such limits that scientists appeared who were experts in only one of Newton's laws, poorly understanding the rest of his laws. In this case, physics, like modern biology, would have been disintegrated into many semi-independent "earldoms" and "states". Now let us pose the following questions: would it be possible in this case for Einstein and his theory to appear? In *such* a scientific community, who could have appreciated his theory and made a realistic choice between classical mechanics and the relativity theory? The answer is obvious: the appearance of Einstein would have been impossible and nobody could have evaluated his theory, as both the former and the latter necessitate understanding of physics as a whole and such *integral* knowledge has to be realized in some *single* head. The role of the personality-creator can neither be substituted by a council of experts, nor by a conference, nor even an international congress. The history of science contains no example of some discovery being made by a symposium, rather than by an individual person or personality. Hence, we contend that only personality can reliably provide knowledge with integrity and logical orderliness. From all the above-said, the unanimous conclusion follows: the scientific method exists only until it, from the first to the last point, can be placed and operated in somebody's head. Under conditions that there is one expert responsible for mastering only of the first Newton's law, while the other one, only of the second law, the scientific methods ceases to operate or even exist, and becomes a myth.

Mythology starts at the time that one mind ceases to encompass the whole subject area under study, after it has been revised refined and generalized as far as possible. To preserve scientific method in a working state, the area of investigation inevitably starts disintegrating, and is doing this precisely as much as necessary for the intellect of one person to be able to operate with it as with a logically closed construction. Whereas from the beginning of the 19$^{th}$ century to the 1960's, the subject of investigation had been the cell, beginning from the 1970's the uninterrupted process of specialization led the cellular theory beyond the limits of competence of an individual specialist. This border is remarkable; it shows the attempts to present a generalized concept of fundamental cell properties (1,4,5,6,9,12,13). The last change of the commonly accepted paradigm in the modern history of cell physiology is connected with the names of Boyle and Conway (1) and Hodgkin (5) through their versions of membrane theory, of Dean (2) with his hypothesis of sodium pump, and of Skou (11) with his suggestion that it is Na, K-activated ATPase that is indeed the sodium pump. Since then, no such massive attempts at theoretical generalization of our knowledge of the cell have already been made, as their volume seemed to exceed significantly the possibilities of the intellect compass of the individual scientist. Let us consider the situation by the specific example of the competing theories.

## TWO COMPETING THEORIES IN CELL PHYSIOLOGY

Whatever aspect of cell activity you try to explain, your consideration will include concepts of i) how some substances penetrate the cell easily, while others have more difficulty, and still others may not not penetrate the membrane at all (the property of semi-permeability); ii) why substances, for instance, $K^+$ and $Na^+$ ions, are distributed non-uniformly between the cell and the medium: some are more abundant in the cell than in the medium, while others, on the contrary, are more abundant in the medium than in the cell (the property of selectivity); iii) by what means the cell generates electrical potential, and iv) how the cell manages to maintain osmotic equilibrium with the medium (osmotic properties). All other ideas about the cell, including those at the molecular level, depend on how you explain these properties. For this reason, the above properties have to be considered fundamental.

There are two approaches to explaining these

properties. The first is the membrane theory – the commonly accepted, dominating theory of our time. Everybody who is interested in biology faces it from the school bench and keeps acquaintance with it in university courses, whereas to scientists this is not a theory, but rather the style of thinking. In other words, whereas the "fathers" of the membrane theory retained a (little bit of the) uncertainty in their thinking, their sons have accepted it absolutely without doubts as the truth in their scientific inheritance.

According to the membrane theory, all four fundamental cell properties are explained by properties of the membrane that separates the cell content from the environment. With such an approach, cell physiology is reduced in fact to the physiology of a film no thicker than 100 Å. From the point of view of the theory, the cell content can be considered as a simple watery solution of cellular components, this solution not differing theoretically from a mixed solution of organic and inorganic components in a test tube. This theory does not need a cytomatrix as a *theoretical parameter*; it needs none of the properties of the cytoplasm and nucleus, but the only necessary ability of the cell contents to "swim" in the solution. Common sense should suggest that at least the minimal doubts that the single plasma membrane alone, with its mass accounting for a thousandth fraction of the whole cell mass is capable of regulating ion composition of the intracellular medium on a scale exceeding a million times its own volume.

Another point of doubt is the existence of a strange exception. If the membrane "theory" is a theory in the same meaning as this word is used in physics (i.e. from a logical, integral system from which deductions can be made), it should follow that *any* asymmetrical distribution of a substance between the cell and medium is a result of activity of a necessary special system of activated transport located in the superficial membrane. However, this attractive theory does not operate. Oxygen turns out to be concentrated in erythrocyte not because it is pumped into the cell by a special pump, but because it is concentrated due to adsorption by hemoglobin. There is no oxygen pump. If so, let us ask a simple question: can it be that nature used the adsorption mechanism only once? The negative answer to this question provides a different approach to explain the fundamental properties of the cell – the Association-Induction Hypothesis (AIH).

Unlike membrane theory, the AIH has only one author – Gilbert Ling (6,8). He believes that the case with oxygen is not an exception, but reflects the general rule: sorption (or its absence) on intracellular structures can play an important role in highly asymmetric distribution of substances between the cell and environment. All four fundamental cell properties are eventually explained by sorptional processes in the cytoplasm and nucleus. The plasma membrane and other cell membranes also are involved in the regulated process of sorption / desorption. Also of importance is that the AIH *needs* the cytomatrix as an organized structure. For this reason, as well as for other reasons, this theory considers the cytoplasm not as "bullion", but as an organized structured system that includes, among other things, cell water which is so often ignored or assumed in other concepts. Essential defects of the AIH are the absence of its own interpretation of the structures that the membrane theory calls channels, carriers, and pumps. This depresses the further development of the AIH and weakens its attraction in eyes of the scientific community. But this lack of development hinges on the fact that this alternative concept has received negligible funding.

## "SICK" SCIENCE

One can become convinced that there has been a sea-change in modern science, which has acquired an essentially different quality from what it had 50-60 years ago, at the period of foundation of the membrane theory and of its competitor, the AIH. With respect to fundamental cell properties, it seems that nowadays the 1st and 4th elements of the scientific method have stopped operating. As a result of specialization, many researchers have left such a level of understanding of cell physiology by immersing themselves in the abyss of the endless diversity of details. The scientists are occupied, for example, in studying molecular or even submolecular structure of some channel, meanwhile their knowledge of membrane theory, of which these channels are components, remains at the level of an undergraduate university course. With the horizon as narrow as the lumen of the channel, identification of problems becomes minimal. It is evident that without the first step, the necessity of the fourth one does not even appear. Meanwhile the *choice* between competing theories is a much more difficult task than merely recognition of the existence of the problem. Thus, the scientific method keeps operating, but its remit or frame for the individual becomes increasingly narrower, and dwell at the feet of molecular detail with little or no integration. In the grander theoretical scale of living processes, scientific method has all but ceased. A few who do extol new encompassing ideas generally find themselves ignored because the army of modern day scientists are too busy with their details to take notice, and the new ideas are debated by too small of faction of the scientific community to appeal to grant giving bodies, who seldom give funds to pursue theoretical work in life sciences. Some rectification, however, may be afoot, as new institutes such as the Bauer Center at Harvard, desperately try to reverse the tide, and meet the problem of finding people who can think in more general terms that

are required for the synthesis needed in formulating "general theories", to continue the analogy with Physics. The greatest problem is that we do not have any theories in Biology that match up to those of classical and modern physics, possibly with the exception of the theory of natural selection.

One piece of evidence in favor of this contention is that there are no monographs in the literature that would explain the fundamental cell properties from consecutive theoretical positions. And whereas we can still say about the fathers (the Newtons) of the membrane theory, nothing remains to be said about its sons (the Einsteins). Instead of large generalizations from the fathers of science, we have a large circle of reviews about *either* biopotentials or problems of semi-permeability or osmotic cell properties, but these problems are *never* considered together in the single work form positions of a logically closed theoretical approach. But even these limited plans of analytical work are too large for the present time. In most cases, the authors prefer considering only *isolated aspects* of the problem. Further evidence for degradation of the scientist's horizon is conversion of cell physiology into *molecular* physiology or physiology of the living molecule. The cell as the whole has become a history. The specialists who graduate from universities know reasonably well the operation of only some part of the cell, and the more limited the sphere of competence of a specialist, the more greatly appreciated such a specialist is. Such terms as "protoplasm" and "cytoplasm" are used increasingly seldom. Papers have already begun to appear in which the even the term "cell" is absent. That is why "sons of science" came into being over the last two decades.

The AIH looks interesting, as its theoretical construction reminds us of a classical physical theory, in which numerous consequences are logically deduced from several initial postulates. In this sense, this is an attractive theory. Logic and integrity of this theory allows one to bring to a single denominator quite diverse factors that otherwise seem to have nothing in common. The logic of this theory becomes the instrument that allows conceptualization of the whole from parts and creates prerequisites for the larger view of the problem; from this, molecules are arranged into a structure, and structures into a cell. *It is much easier to master a logically harmonious theory*. Such theory can easily become an instrument of thinking of one individual who will raise the scientific method above the Brownian movement of molecules and will provide some foundation for new theoretical generalizations. In the AIH, it certainly can be traced the structure of the "Greek approach" to the construction of a theory, as opposed to the "Babylonian" tradition. The Greek method was to construct theory on the basis of axioms, while the Babylonian method was a theory representing a complex of individual examples (3).

The evidence for the AIH fruitfulness is that its logic has brought about non-standard experimental approaches, posing interesting experimental tasks. The AIH potential is also indicated by Ling's monographs, in which the author considers both foundations of the theory and its applications to explain various physiological mechanisms at the level of cell and of individual structures. The theoretical integrity of the AIH reveals hidden defects of the membrane theory (7). With all the supposed successes of the membrane theory, *it is misguided if not wrong to lose a critical attitude to it*. The blind faith in its truthfulness can only lead to accumulation of methodological and theoretical mistakes, which in the long run will reduce efficiency and progress of science. It is always important to remember that there are no theories that would not have to face the awkward little fact that contradict them (10).

We also see the painful symptom in that the available experimental evidence in favor of the AIH is *ignored* by the scientific community. There are neither checks, nor arguments against it, nor analysis of the theoretical AIH non-justifiability. Meanwhile, we are dealing with publications of Ling and other independent authors in prestigious scientific journals. Ignoring the issue itself destroys scientific method and destroys science as an instrument of obtaining reliable knowledge. It would be much more useful for the scientist to know two idioms, that of the membrane theory and that of the AIH. If experiments had been carried out taking into account the methodological requirements of both concepts, the appearance (phantom) of truth would not be threatening science. The play would have been fair, and if so, then let the stronger win. But to whom will come the idea of studying these metalanguages of cell physiology, if general attention is completely paid to details and the horizon of thought is measured in nanometers?

## CONCEPTUAL HALLUCINATIONS

The bearers of hypotheses and theories always were the vanguards of science, its real creators; however, the sphere of their competence is constantly narrowing at the epoch of specialization. Narrow specialists also become limited people. The generation of scientists with a large circle of theoretical interests abandoned science long ago. Nowadays, even Nobel Laureates are specialists of a narrow profile. Similar specialists also are reviewers determining standards of the modern scientific literature. An important question arises: who at our time is able to appreciate the completeness of the correspondence to facts relating to the membrane theory that formed half a century ago? Who can make a choice between the membrane theory and the AIH, or any other competing theory?

The answer to all these questions is that nowadays there is nobody to make such choice. For as long as several

decades, the sons of science have come to believe in the infallibility of their fathers and cast no doubts on the membrane theory, at least because they do not master it. This belief that contradicts the spirit of science, which accepts nothing by just taking on trust, will inevitably lead with time to conversion of the membrane theory into "conceptual hallucination". And this could be true not only for the membrane theory. Any large generalization of the past and present, with time, could become the hallucinatory, as science becomes fractionated into more and more minutely focused areas of investigation. Einsteins of the cosmic scale are replaced by einsteins of nanostructures. And as the intellectual narrowness continues to deepen, the number of hallucinations will rise. The attitude towards scientific method will be that it is a myth.

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