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Review

Outline of a concept for organismic systems biology

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ABSTRACT

For several decades experimental biology and medicine have both been accompanied by a dichotomy between reductionistic and anti-reductionistic approaches. In the present paper it is proposed that this dichotomy can be overcome if it is accepted that research on different organizational levels of the organism is necessary. The relevance of such an approach becomes much clearer using an appropriate concept of the organism. The proposed concept is called "organismic systems biology" and is a compilation of three related theories, which are basically in line with considerations of many other organismic thinkers. However, it is argued, that this integrated concept is able to clarify basic assumptions of organicism. The theories are: the systems approach of Paul Weiss, the developmental systems theory and the theory of increasing autonomy in evolution. The hypothesis is that the different levels of organismic functions, which are described by these theories, are necessarily interrelated, thus generating the autonomy of the organism. This principle of interrelation needs to be regarded in scientific reasoning and can be crucial for solving many medical problems.

1. Introduction

There is a long standing debate in the diverse fields of life sciences about the relevance and significance of reductionistic versus holistic concepts of research. These views form different approaches to understanding organisms and influence research programs, interpretations of experimental results and medical interventions in a very profound way. This discussion has been more intensive in biology [1–7], however, in medicine it has been of fundamental importance as well [8–15]. For further readings see [16].

I agree with Brigandt and Love [16] that the thereby generated reductionism versus anti-reductionism terminology has tended to create a false dichotomy between two extreme positions: on the one hand reductionism as the idea that molecular biology can in principle *fully explain* all biological facts – making higher level biological theories dispensable – and on the other hand anti-reductionism as the idea that higher level biological fields possess explanatory principles of their own in the sense of *not benefiting* from molecular biology. Between these two extremes a variety of intermediate positions exists that has motivated many of the efforts seen in alternative as well as in conventional research programs. I will propose that the task of science on different levels of organization becomes much clearer if we use an appropriate concept of the organism.

In recent years critical discussions by some scientists have again arisen upon the assumption that today's biology is due for a conceptual revolution, that it needs to develop a new framework to describe life in a way that better matches the actual properties of the organism and of life itself [3–5,10,17–22]. However, the described dichotomy and the difficulties of some of the older standpoints are seen as a search for something like a new synthesis, not a revival of the old debates. What is being questioned are not the results and the significance of molecular research in itself, but rather the one-sidedness in focusing exclusively on chemical and physical processes with the expectation that living systems can be fully explained from this perspective. This also includes the widespread analogy that sees the organism as a machine and its functions as "mechanisms". Major setbacks and unfulfilled expectations increasingly suggest that these critiques are justified and point to a central problem of modern life sciences.

Woese [3] requests "a new biology for a new century" and assumes that the extreme reductionism developed in many disciplines of biology during the 20th century might have been a necessary and unavoidable transitional stage in the overall course of biology. However, "a biology viewed through the eyes of fundamentalist reductionism is an incomplete biology. Knowing the parts of isolated entities is not enough. A musical metaphor expresses it best: molecular biology could read notes in the score, but it couldn't hear the music. . . . The time has come to replace the purely

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reductionist 'eyes-down' molecular perspective with a new and genuinely holistic, 'eyes-up' view of the living world, one whose primary focus is on evolution, emergence, and biology's innate complexity." (p. 175).

Similar views are shared by many molecular biologists today and this has fueled the widespread interest for systems biology. However, I will argue that the common approach to systems biology appears to be fundamentally flawed and does not really overcome reductionism.

Woese [3] continues: "Let's stop looking at the organism purely as a molecular machine. The machine metaphor certainly provides insights, but these come at the price of overlooking much of what biology is. Machines are not made of parts that continually turn over, renew. The organism is. Machines are stable and accurate because they are designed and built to be so. The stability of an organism lies in resilience, the homeostatic capacity to reestablish itself. While a machine is a mere collection of parts, some sort of 'sense of the whole' inheres in the organism, a quality that becomes particularly apparent in phenomena such as regeneration in amphibians and certain invertebrates and in the homeorhesis exhibited by developing embryos." (p. 176).

Polanyi [23] deals with these questions in an absolutely visionary paper already in the late 1960s.

Richard Strohman, as many authors before him, focuses especially on genetic reductionism which maintains that all processes of an organism can finally be reduced to the level of the gene and that the gene is the ultimate control agent. He leaves no doubt about how important the discoveries of genetics are. However, he does state that the original concept to study genes has illegitimately been extended to explain the whole organism [24]. This is especially demonstrated by the results of recent genetics, which show many anomalies that do not match with what has been expected from a gene centered view. Strohman wrote " . . . Cell and molecular biology, in conjunction with new theoretical developments, have, in the past decade, taken us from a grossly naïve view of genetic determinism (that complex traits are caused by a single gene) to the stark reality that almost all human diseases are complex context-dependent entities to which our genes make a necessary, but only partial, contribution."(p. 701).

Next, I propose an outline of an organismic theory which avoids the one-sidedness of reductionism versus holism. Organicism is the point of view that living organisms are complex, hierarchically structured systems, whose parts are all functionally integrated into and coordinated by the system. This view is shared by many scientists who are looking for a more appropriate approach to the phenomena of life. Organicism brings thinking about organisms closer to the actual phenomena of life. To achieve this I do not invent some new model or theoretical construction, but use insights organismic thinkers have often formulated before, but which have hardly been regarded seriously in mainstream biology. Basically these ideas were developed from empirical experience rather than theoretical considerations. It is a sort of synthesis of the work of some researchers, who were not convinced by the assertion, that organisms, including humans, are nothing more than a product of their molecules, a mostly unexpressed und unconscious claim that dominates large fields of science today, but has never has been proven.

The concept will be compatible with the empirical knowledge which has been gained by today's research programs. However, some interpretations will look different due to this concept. Thus there is no conflict with them but rather the knowledge will be adjusted to its appropriate place.

Essentially the concept refers to three theories, which have a common denominator although they are formulated from different perspectives. Subsequently I will discuss the relevance of the synthesized theory for biology and medicine as well as its difficulties. Then I shall argue that a renewed and much more appropriate research program is accessible for "a biology of the new century".

2. Analysis and synthesis

The first one of these theories comes from Paul Alfred Weiss (1898–1989). He was an Austrian scientist who moved to the United States, where he became a leading figure in science of his time [25]. His contributions to neurophysiology and developmental biology are well known. However, curiously enough his systems approach is nearly forgotten. Only occasionally is his concept cited, but there has hardly been any understanding of this fundamentally unique approach, which differs essentially from most of the usual approaches of systems biology today. Only recently there have been publications which appreciate the concept in a more profound way and argue for a revival of his ideas [26–28]. In the present volume Drack and Wolkenhauer also include the common ground with the work of Bertalanffy [28].

I propose that Weiss comes quite close to what the basic features of an organism really are (see [27] for more information about the history of his ideas). However, it is most impressive that recent research results step by step support his view. Or formulated the other way round: many results become better understandable in the light of his approach.

Weiss develops a perspective, which is suited to understand the organism as well as organs and cells as integrative units, a notion still poorly understood and largely neglected in biomedical science [29–36]. Weiss characterizes the relation of analysis and synthesis and describes how we first recognize nature as an immense cohesive continuum. Then we start to identify discrete fragments in it and isolate single entities to learn more about their exact properties. Subsequently we find out that modifications of such an entity, that may be called entity A, are regularly associated with a series of modifications in another entity called B. By studying this regularity a rule can be established from which all future correlations between A and B can be extrapolated. We then proceed to study A in its relation to C, and C in its relation to B, and so on, to learn how different parts of nature, erstwhile mentally dissected and separated, are actually interdependent. At this stage it is expected that it should be possible to turn the process around – either physically or mentally in our imagination – linking by way of consecutive synthesis such coupled pairs into complex chains and cross braces, reconstructing the whole system in a quasi-mechanical way.

As Weiss explains, in practically all of our biological thinking the opinion still dominates that by application of this synthetic method science will eventually succeed in describing and comprehending all entities and processes in nature. Weiss states that physics has already begun to depart from such a micromechanistic attempt whereas biology has not. However, in an organism the mere reversal of the analytic dissection can yield no complete explanation of its behavior as a living system.

What is overlooked is that during isolation of A, B, etc. already a lot of information has been neglected in order to characterize these entities. However, especially in an organism, each entity depends upon the interactions with others. This means that in the absence of C neither A nor B can exist. The coexistence and co-operation of all three is indispensable for the existence and operation of any one of them. Only by artificially neglecting the so-called boundary conditions can A and B be studied in an isolated manner.

Experimentally, this procedure may often be adequate. Nonetheless, it is overseen that the information which is neglected during this process cannot be reconstructed through a synthesis from the knowledge of the properties of these parts. The analytical procedure has been very successful in science, but obviously it must