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A MODERN CONCEPT OF THE "CELL THEORY"
A PERSPECTIVE ON COMPETING HYPOTHESES OF STRUCTURE[1]

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According to the "cell theory" in its original form, morphogenesis in multicellular organisms results from oriented cell divisions and cell growth. This view is based on the still-valid fact that cells represent the smallest structural and functional units exhibiting all fundamental properties and manifestations of life. Each cell stores, replicates, and partially expresses the genetic information of an organism. Recombination and syngamy take place at the cellular level, and sexual reproduction of multicellular organisms depends on single cells. Nevertheless, morphogenesis in multicellular organisms is governed by supracellular factors. This basic tenet of "organismal theory" is demonstrated best by plasmodial organisms such as siphonal algae that can be structured to a certain, if limited, extent in the absence of individualized cells. It seems improbable, though, that "cell theory" and "organismal theory" represent true alternatives. Multicellular organisms are not merely aggregates but nonlinear systems of cells with emergent characters. Typological and finalistic "explanations" are not, however, intended to clarify causal connections. The formulation of a unifying concept appears to be hindered not only by obsolete historical reasons but also by conceptual differences and also by methodological barriers. Concerning the balance of genetic and epigenetic factors in morphogenesis, it appears unlikely that information stored in one-dimensional nucleic acid molecules could suffice to direct ordered three-dimensional development.

Introduction

In 1879 Anton de Bary formulated the frequently quoted sentence, "It is the plant that forms cells, and not the cell that forms plants" (my translation). This sentence is acknowledged as the basic tenet of the so-called organismal theory or plasma theory in morphogenesis of plants, and of multicellular organisms in general. Originally, this "theory" was meant to be an antithesis to a still older postulate that the morphogenetic processes in the microscopic and macroscopic domain were just the result of oriented cell divisions and vectorial cell growth (Cremer 1985; Sander 1989). The discord between "cell theory" and "organismal theory" still smolders (Hagemann 1982; Sitte 1982; Kaplan and Hagemann 1991). I will discuss it here from the viewpoint of contemporary cell biology.

Cells as the elementary units of life—and of morphogenesis

Macroscopic morphology can be pursued successfully without knowing anything about cells. Goethe's discovery of the human intermaxillary bone and the foundation of phyllotaxis by Franz Schimper and Alexander Braun are well-known evidences. However, for about 150 years cells were shown to be the building blocks of almost all organisms, small and large. Thus it appeared tempting to reduce morphogenetic processes conceptually to corresponding events of cellular growth and multiplication. This was made even more tempting as the single cell appeared as the smallest unit of life, in that all essential characters of living beings can be found at the cellular, but not at the subcellular, level. In 1858, Rudolf Virchow in his famous *Cellularpathologie* was able to demonstrate that many diseases can be investigated and explained on the basis of cellular disorders.

It was in this general mood that statements such as the following could be expressed: "Each higher plant is an aggregate of fully individualized and isolated living beings, i.e., of cells" (Schleiden 1838); "The reason for nutrition and growth rests not with the organism as a whole but with the individualized elementary particles, i.e., with the cells" (Schwann 1839); "In plants, the entire physiology can be reduced to the life of the plant cell; and the vital functions of complete plants, inasmuch as they cannot be deduced from cellular functions, are almost negligible" (Schleiden 1842) (my translations).

Reductionistic exaggerations of this kind cannot be defended today. Yet it is to be maintained that macromorphology, too, needs to take notice of cellular functions and processes wherever this is possible because cells are not just arbitrary substructures of macroscopic organisms but are endowed with a series of particular characters that should not be overlooked when dealing with living beings. Although most of the basic cellular characters are commonplace, it might be helpful to make a brief inventory of them:

1. Every normal cell respresents a "minimal space" within which all indispensable organelles are contained. Less than a cell is obviously not enough for the perpetuation of the living state;

[1] I wish to express my gratitude for the invitation to this symposium. Professor Katherine Esau was, through her famous book *Plant Anatomy,* among my most admired academic teachers.

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and more than a cell is not absolutely necessary, as is demonstrated by the protists and also by permanent cell cultures. A cell is a "quantum" unit of life.

2. Each cell or, in coenobia, each energide consisting of a nucleus with its surrounding cytoplasm, contains at least one complete genome of the respective organism. Consequently, big organisms contain their specific genetic information not just once, or in a few copies, but as many times as there are nuclei containing cells in them. In a full-grown human this number is more than 10,000 billion. One of the most basic functions of all living beings, namely, replication of genetic information and its transmission, is effected by single cells even in the biggest multicellular organism.

3. The single cell is the unit of recombination and syngamy, and hence, of sexuality. Accordingly, the life cycle of any plant or animal commences with a single cell. For sexual reproduction, all multicellular organisms produce single-celled gametes, a few of which then fuse to form single-celled zygotes.

4. It has been observed for one and a half centuries without exception that cells are strictly sui generis—cells can only arise from their like, at least under present-day conditions.

5. The cell is the smallest unit of differentiation. While this is often masked by concerted and parallel differentiation of multicellular complexes, it can, however, be seen very clearly in unequal cell division and alternative differentiation of juxtaposed cells, e.g., in the formation of idioblasts. Certain cells in a tissue can be, in contrast to their neighbors, extremely elongated, e.g., fiber cells and nonarticulated laticifers. Similarly, single cells within a tissue may be subjected to programmed cell death as exemplified by tracheids and tracheary elements.

6. Cells are the elementary units of regeneration. This fact has gained enormous practical importance in the cloning of flowering plants. On the other hand, most tumors originate from single transformed cells. Cancer is primarily a cellular disease. It has, however, macroscopic consequences in the form of an entirely disordered morphogenesis.

7. Life has existed on earth for more than 3.5 billion years (Schopf 1983), yet about 80% of the evolution of life took place at the level of single cells. The enormous diversity of present-day protists (Margulis et al. 1989) might be a late reflection of this.

8. The origin of new forms of life by symbiogenesis was possible only at the level of single cells. According to the endosymbiont theory, the transition of prokaryotes to eukaryotes was achieved by the incorporation of aerobic, or photosynthetic, eubacterial cells, fitted with F-ATPases (ATP synthases) into larger fermenting and phagocytotic cells. Intertaxonic combination, i.e., the endocytobiotic incorporation of unicellular symbionts into bigger host cells, can be repeated, and cells exist that are composed of up to seven different cells encapsulated into each other, thus forming new biological entities (Sitte and Eschbach 1992).

9. It seems to be a general principle in nature that diversity is achieved not so much by entirely new developments but by combining preexisting elements into larger complexes. This "unitized construction" is exemplified by, among many other things, the formation of atoms from a few elementary particles, of innumerable molecules from a relatively few kinds of atoms, or an unlimited number of polymers from limited types of monomers. About one million different antibodies of the human immune system are encoded by stochastically combining less than one thousand short DNA sequences that in turn belong to not more than five different classes. Similarly, the enormous number of different species of eukaryotic organisms may be looked at, in a certain sense, as the result of a different combination of cells that, in their part, are only of limited variability. It is not so much the size or the structure of cells that is varied, but their number.

An interdisciplinary side-glance

Plants differ from animals in many respects, and accordingly, the typical plant cell is very different from a typical animal cell. Yet the basic problem of morphogenesis is principally the same in humans, animals, fungi, plants, and larger algae: genetically identical, or nearly so, cells become different in such a way as to ensure the formation of the species-specific overall shape and also the specific physiological and ecological properties of a particular organism.

Higher animals, and mammals in particular, are individualized partly because of their mobility in a far stricter sense than higher plants. By the formation of a skeleton from fibrocytes and bone cells, the formation of a system of microscopic boxes as a means of stabilization becomes irrelevant. In fact, the majority of animal tissue cells do not possess rigid walls, and as isotonocytes they do not develop an appreciable turgor pressure. Their flimsy surface layer, or "glycocalyx," does not stabilize the cells but serves entirely different functions, such as prevention of undesired cell fusion; yet the body of mammals is built of individualized cells. Even in systems of extreme supracellular integration, as in the central nervous system or the immune system with its many kinds of circulating cells, the individuality of the single cell is maintained. And what is more, it is the individuality of the cells involved

that ensures the proper functioning of the whole, and enormously complex, system.

"Big-cellers" versus "multicellers," and the limits of the cell theory

The evolution of organisms with exceptionally large cells apparently has been adopted in several lines independently. Unicellular organisms of this kind attain macroscopic dimensions and a remarkable morphologic diversity that may lead to complicated structures such as the ones of the siphonal green algae *Acetabularia* and *Codium*.

The size of nuclei is correlated with the nuclear DNA content and hence with the *C*-value of a given species, but the volumes of nucleus and cytoplasm exist in a fairly constant proportion to each other. Accordingly, typical big-cellers (e.g., *Caulerpa, Valonia, Botrydium,* and *Vaucheria*) possess an all-comprising plasma membrane and cell wall, and usually also a large central vacuole, yet they contain numerous nuclei of entirely normal size within an enormously augmented mass of cytoplasm. Not only the nuclei but also all other cell organelles are increased in number but not enlarged. This fact prompted Julius Sachs in the last century to coin the term "energid." Sachs (1892) defined the energid as a nucleus together with the portion of cytoplasm that is "dominated" by that nucleus. Cells with a single nucleus are to be regarded as "monoenergidic," whereas coenobia are "polyenergidic."

Sachs's concept is not just abstract thinking. This is demonstrated by the fact that many polyenergidic systems can be transformed very rapidly into monoenergidic ones by dissociating the coenobial body into many single cells, each with a single nucleus. If, e.g., the habitat of the siphonal xanthophycean alga *Botrydium granulatum* is flooded, countless zoospores are formed and liberated by autolysin-mediated rupture of the original cell wall. Similarly, cysts and gametes are produced in *Acetabularia* once formation of the "umbrella" has been accomplished. Comparable situations are encountered in early developmental stages of insects (Fullilove et al. 1978).

Nevertheless, with regard to morphogenesis, it is clearly demonstrated by the "siphonal" organisms that the overall shape cannot just be the result of the morphogenetic activities of single energids. Rather, there must exist superior, and integrating, systems of morphogenetic vectors and controlling centers that are not identical with single energids. The siphonal alga *Vaucheria,* e.g., exhibits vigorous protoplasmic streaming by which the countless nuclei are steadily moved around. Consequently, neither they nor the streaming endoplasm can be responsible for morphogenesis, which in *Vaucheria* consists of simple, yet well-ordered, ramifications of the cylindrical thallus. Examples of this kind mark the limits of any kind of "cell theory": morphogenesis cannot be understood and explained in a reductionist manner by assuming a loose cooperation of otherwise individualized single energids or cells.

Cell theory versus organismal theory: a real alternative?

In the history of science there are many examples of controversies that were concerned with apparent as opposed to real differences. In all these controversies one side was not necessarily wrong and the other right but, rather, both sides were right, if often in a somewhat restricted sense, and the original mistake was that the wrong question had been asked and that differing explanations had been looked upon as real discrepancies. "Problems" of this kind, appearing paradoxical at first, could often be resolved by combining thesis and antithesis to achieve a fruitful synthesis. Well-known biological examples of this kind are the old "chicken or egg" problem, or the endless dispute between preformists and epigeneticists, and again between mechanists and vitalists, continued today between reductionists and holists.

The contradiction between "cell theory" and "organismal theory," too, may turn out to be artifactual. Both sides have convincing arguments in their favor that nowhere contradict each other directly. If obsolete and untenable overstatements (as those of Schleiden [1838, 1842] and Schwann [1839], quoted above) are no longer considered, cell and organismal theory could well appear as concepts that complement each other. These theories may be looked upon as the result of different starting positions, or different methodological approaches, and hence of different viewpoints, but not as contradicting doctrines of which only one can be correct. The ultimate resolution of these two theories must await an in-depth comparison of them, their assumptions, predictions, and especially, their inadequacies.

Supracellular morphogenesis results only from supracellular determining patterns and corresponding factors to which single cells respond. These must be supplied with correct signals from their surroundings so that they can behave accordingly (Müller 1979; Marx 1991; Melton 1991). Signals of this kind often concern a great number of cells. But even with these cells, the single cell appears as the smallest unit of response. Hush et al. (1990) recently published a very impressive example of this. As soon as supracellular signals are to be investigated, research cannot remain fixed at the single cell. Some supracellular signals are already known in detail. The existence of a great number of other factors of this kind have to be postulated, especially for pattern for-

mation in plants (Stevens 1974; Sitte 1984; Steeves and Sussex 1989; Sachs 1991), yet remain to be explored.

At any rate, each multicellular organism represents a typical system. Systems, with regard to their functions, are certainly more than the mere totality of their parts. With respect to mass and volume, the cells are additive parts in a multicellular system. Concerning the function(s) of such a system, however, the connections of the parts are multiplicative. Systems of any kind invariably exhibit characters that cannot be attributed to single, isolated parts of the system (Mohr 1990).

By applying all this to our present problem, one must say that it is not the single meristematic tissue or cell that represents the biological "unit" but the whole multicellular organism that consists of cells and to which the cells are, however, subordinated. Still, it is the cells that respond to coordinating signals. The problem is reminiscent of the old question of whether the nucleus governs the cell or, rather, is governed by the cell. Here, at least, the solution is clear: both answers are correct.

Genetic continuity—other than by nucleic acid molecules?

The problem dealt with here not only concerns supracellular structures but also single cells, many of which perform complex morphogenesis (Drubin 1991). What is more, this general problem has received an entirely new dimension through the fantastic achievements of molecular biology. No doubt, genetic factors can greatly influence morphogenesis. However, the question of whether the genome of a given organism comprises the complete information necessary for the orderly development of that organism is often answered quite differently: most molecular biologists would give a positive reply, whereas most embryologists would demur.

Morphogenesis in multicellular systems means cellular differentiation. Differentiation in turn depends upon vectorial determinants such as morphogenetic fields, gradients, or polarity. However, gene products in general exhibit the properties of scalars. After their production, their proper alignment and incorporation in growing and multiplying cells rests upon the preexistence of appropriate vectorial "pre-patterns." The preformists of today emphasize the role preexisting patterns play in the generation of new structures of successive developmental stages: *structura e structura.* Modern epigeneticists, however, are exploring the possibilities of a de novo generation of gradients and symmetries (Meinhardt 1982).

There is a wealth of examples of pattern formation according to instructions provided by preexisting patterns, among them, of course, replication and transcription of DNA. However, genetic continuity is also possible without nucleic acids. At the molecular level this is exemplified by biomembranes. Although lipid bilayers can be produced easily by a simple entropic self-assembly of polar lipid molecules in a polar medium, until now no de novo formation of biomembranes has been observed in living cells. Rather, biomembranes are always derived from preexisting ones by incorporating new lipid and protein molecules into a biomembrane, followed by the separation of part of this membrane by membrane flow (Sitte 1979).

Corresponding situations are also encountered at the cellular and supracellular level. Isolated somatic cells of higher animals may give rise to cell and tissue cultures, but entire animals will never come about from such cell cultures, despite the presence of the genetic information in a basically unchanged form. Apparently there must be additional, and essential, instructions that had been available in the fertilized egg but are no longer in the somatic cells derived from it. If the microtubular cytoskeleton of moss spores is destroyed by colchicin, the affected cells can still grow, but they are unable to divide unequally as they would have to in order to develop into the moss gametophyte. There are countless examples of monstrosities that obviously did not result from a genomic disorder. Many misled morphogenetic processes can be provoked artificially without employing mutagenesis. Well-known botanical examples of this kind are allomeric leaf arrangements in whorled phyllotaxis, pelories, and fasciations of twigs.

From these few examples it can be seen that there must exist, besides the genetic continuity of one-dimensional DNA molecules, an entirely different "epigenetic" continuity of supramolecular, and sometimes even supracellular, patterns that, quite in contrast to the genes, change dramatically during individual development but nevertheless return to comparable starting positions in every life cycle as, e.g., in egg cells, spores, and during regenerative processes. If these two- and three-dimensional patterns are destroyed, further development will be abnormal or blocked, without mutation of a single gene.

Within such a superior framework the genes are, of course, indispensable factors (Coen and Meyerowitz 1991), but not the only ones. For comparison: with a switch one can turn the lights on and off, which is not possible without that switch. But the switch can function only if some other necessary factors are working, the power plant, the power transmission system, a functioning lamp, and so on. Similarly—this is my proposition—the orderly functioning of genes might rely on an "infrastructure" that for its part cannot be established by the mere functioning of genes (Bock and Marsh 1991). What can isolated

DNA molecules really do? Almost nothing, as demonstrated, e.g., by virus particles. The more we approach molecular and atomic dimensions of living beings, the less we see of larger and more complex structures. Maybe the genetics of tomorrow will look quite different from the genetics of today.

Why is there a gap between cell and organismal biology?

If there is no real contradiction between cell and organismal theory, why then can these theories not be combined? There appear to be two obstacles, one conceptual and the other methodological.

The conceptual obstacle arises from the difference in the importance attached to the search for causal connections in cell and molecular biology on the one hand and in gross morphology on the other. In terms of a general theory of science, cell and molecular biology may be characterized as experimental and analytical approaches, whereas macromorphology is holistic and synthetic. In this latter domain, comparative studies prevail, often from a finalistic or teleonomic perspective. This is, of course, understandable, as morphogenesis is an extremely complex process, the investigation of which faces enormous technical difficulties. Nevertheless, it is possible. It is amply demonstrated by the amazing progress in the developmental biology of animals how much can be achieved by a determined application of modern cell and molecular biological methods to a few selected model systems, the morphology of which had been known in all details (Evered and March 1989; Jäckle et al. 1989; Wall 1990; Lawrence 1992).

As for the second, the methodological, obstacle, specialization in science not only concerns concepts but even more so the techniques used. By any kind of analytical approach, interactions that characterize the whole are most often destroyed. Plant morphologists, although knowing what questions should be attacked and what objects might be optimally suited for a particular investigation, normally do not have proper equipment and know-how available to solve problems at the cellular or molecular level. If, e.g., the proper coordination and cooperation of cells is of prime importance in supracellular morphogenesis, the question of contacts between cells is of prime importance. But what do we actually know except in a few special cells of the direct coupling of cells, of plasmodesmata (Robards and Lucas 1990; Tilney et al. 1991), of surface receptors, of tissue hormones, of mediators for signal transduction, of the physical isolation of cells? As I would suspect, we simply do not know enough yet. Under these circumstances, a closer cooperation of plant morphologists with plant cell and molecular biologists is imperative.

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