Toward a theory of cellularity—Speculations on the nature of the living cell

> The modes in which the earlier truths of science are preserved in its late forms, are indeed various. From being asserted at first as strange discoveries, such truths come at last to be implied as almost self-evident axioms. (Whewell 1872, p. 45)

Why do cells exist? Is there an obligate relationship between life and cellularity? Certainly there is no exception to the observation that all life on earth is cellular at some stage. Even viruses depend on the machinery of the host cell to complete their life cycles. Evolutionary theory, too, is rooted in the realization that all cells come from pre-existing cells (Virchow 1858), so it is not surprising that the concept of cellularity lies at the center of biological thinking. But to what extent do current concepts of the cell limit our ability to understand its role in organismal development?

Biological knowledge is a mosaic of general concepts or theories, empirically derived observations or facts, and a supporting vocabulary. Although much of this knowledge is of relatively recent origin (in particular the details of cellular metabolism and heredity), many of the concepts date back two and three centuries ago, to the first scientific inquiries into the nature of living things. One may suspect, therefore, that what we take for understanding may sometimes be an illusion produced by the accumulation of layers of terminology, each built on previous usage and therefore circumscribed by it.

The word "cell," for instance, harks back to Robert Hooke's (1665) first use of the term to describe the empty compartments seen in cork (Figure 1). Later, as cells were found in all living things, the word came to embody the universal and fundamental unit of life, which in a modern vernacular might be called the "quantum of life" (Sitte 1992). For today's biologist, the word "cell" carries a complex and far-reaching connotation, conjuring images of a unit of cytoplasm that contains a nucleus and a variety of subcellular organelles and is surrounded by a membrane (Figure 2). In the end, however, although the concept of the cell brings to mind the myriad coupled processes and structures by which the cell controls its own activities, responds to external signals, and maintains continuity between successive generations, we still regard the cell as simply a complex microscopic object. Therefore, our ability to move to a new level of understanding of the cell and of cellularity may be constrained by the vision that we have inherited from our predecessors.

That there are limits to the understanding of cellularity is evident from the fact that there is no formal discipline of cell theory. The treatment of the cell in biology courses is largely confined to detailing what goes on within cells and avoids any attempt to infer unifying general principles of cellularity. A theory of the cell that embodies such unifying principles might tell us why cells exist at all, why some organisms appear to be released from the constraints of cellularity at certain stages in their life cycles, and what the roles of the cell in multicellular development are and how these roles evolved.

In this article, I begin to construct a model of the cell that provides a basis for a conceptual approach to cellular interactions in multicellular organisms. I confine my discussion to plant cells and tissues for two reasons. First, questions of nearest neighbor relationships are more easily and unequivocally resolved in plants than in animals because plant cells do not move with respect to each other after division and because differentiation in plant tissues tends to proceed sequentially, on a cell-by-cell basis. Second, I believe that when considered against the full range of developmental mechanisms that have evolved in plants and animals, the devices available to plants represent a more elemental stage in the evolution of the multicellular habit of growth. It therefore behooves us to model the simpler case before proceeding to discuss the more complex one. I have little doubt that the basic propositions that I suggest here may apply to animals as well as to plants, but they may be overlaid by mechanisms of higher order or promoted to domains of control that extend beyond the level of the individual cell. Indeed, these higher-order mechanisms may apply to plants too. However, because of the immobility of the cells and the sequential mode of growth typical of plants, the simpler modes of differentiation and intercellular specialization still remain visible.

Concepts of the cell

The language that we use needs to reflect and enable the work at hand. How can we begin to formalize the relationship between a cell and its environment? A brief inventory reveals that a spectrum of such relationships is possible. A single, free-living cell "sees" the external world directly across its plasma membrane—a world of resources and threats over which it has little if any control. It responds to a variety of incoming signals directly, recognizing and processing substrate molecules as they approach and pass through the plasmalemmal interface. It is functionally self-reliant, requiring the presence of no other cells to remain viable.

For a cell that is part of a multicellular organism, however, the view

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trated and highly coupled biochemical engine (the automaton), a complex system whose description requires the synthesis of the most rarified concepts and terminologies (Kauffman 1993). At the same time, it is apparent that there must be a reconciliation between the two at the cell surface so that irrespective of differences in complexity and order between processes at work in the interior of a cell and those at work in its environment, the two are finally brought into some kind of equivalence at the boundary.

This reconciliation between internum and externum would seem to be one of the prerequisites for the viability of the system. An incoming signal whose appearance at the externum is not reflected in some reconfiguration of the internum is nonexistent as far as the cell is concerned and can be ignored. I have termed this correspondence Sands' Principle of Equivalence (Figure 5), which implies that some form of equivalence or complementarity between internum and externum is a sine qua non of the living state. The ultimate challenge is therefore to define the components of this equivalence, thereby establishing a basis for modeling and characterizing the interactions between the cell and its environment, the cell and neighboring cells, and the cell and the whole organism.

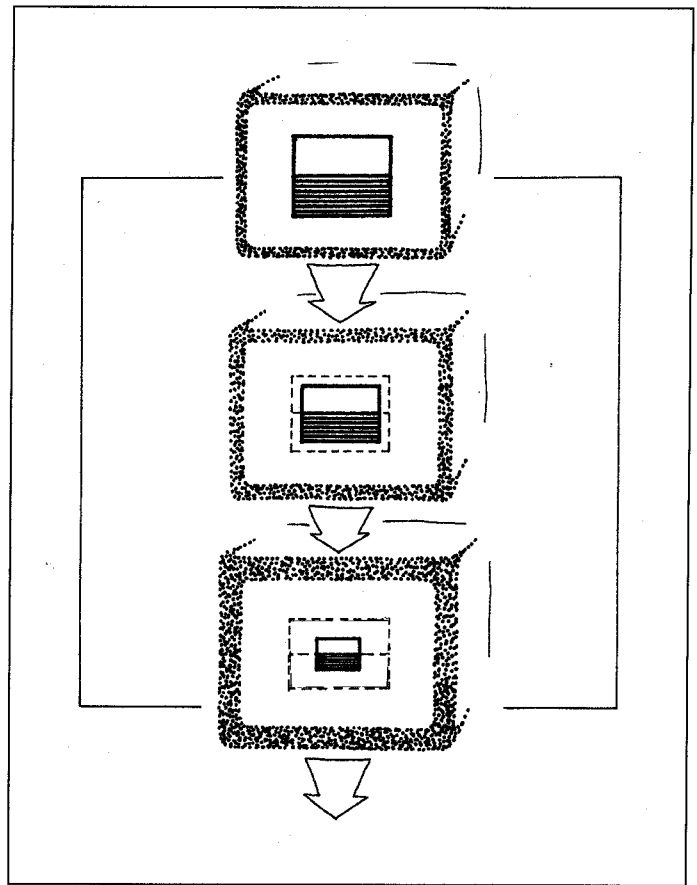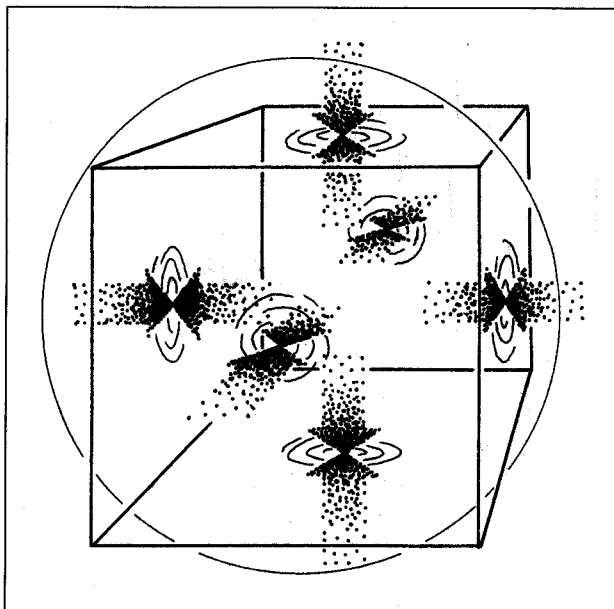**Differentiation.** As biologists, we have inherited another terminology

from our standard bearers—that associated with the idea of "differentiation." This term encompasses some of the most universally accepted notions in all of developmental biology, and yet it is one that is often used without being clearly defined.

What is cellular differentiation? A quick answer is that it is any process by which a cell changes in some respect and becomes different. But now we must ask: different from what? By differentiation, do we simply mean that a cell becomes different from what it was—namely, some "undifferentiated" starting condition? Or do we mean that two initially identical cells diverge in their capabilities so that they become different from each other? Clearly we can mean either, and yet it is also clear that these two alternatives can imply quite different cellular processes. In fact, there are three basic types of differentiation, each of which has different implications in terms of cellular process (Gurdon 1974).

• Autodifferentiation. Perhaps the most basic kind of differentiation is that which is characteristic of the prokary-
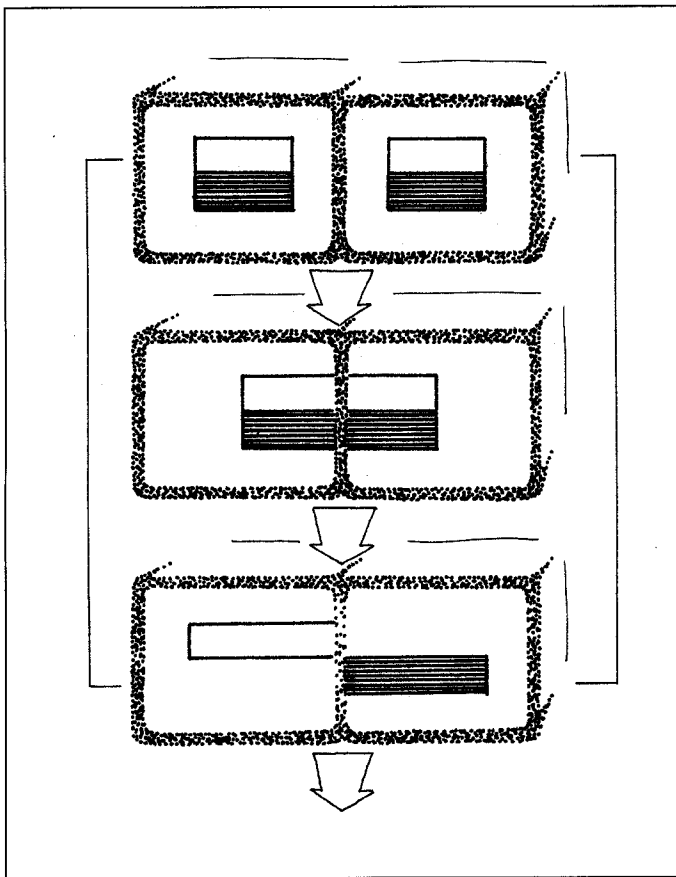


Figure 6. Autodifferentiation. The formation of a resistant spore in which two vital cellular functions, represented by two boxes (shaded and open), are down-regulated to the minimal sustainable level and a thick, resistant spore wall is deposited. The boundary becomes relatively impermeable. Correspondence between internum and externum is reduced.

otes, in which a cell differentiates to form a resistant structure that is capable of surviving adverse conditions or serving as a propagule that can be carried some distance without the need for a substrate. In this type of differentiation, a single cell, initially fully active metabolically, secretes a resistant wall, accumulates storage products, slows its cellular processes, and essentially shuts itself off from the outside world (Figure 6). In this state of dormancy, it is clearly different from what it was at the start, and so the term "differentiation" may be appropriate. In a more general sense, the term "autodifferentiation" implies a kind of differentiation that can proceed without the presence of any other cell.

• Eudifferentiation. Now consider the case of two adjoining cells, initially derived from the same meristematic or blastemic cell line, which gradually diverge in function so that

Figure 5. Sands' Principle. The correspondence between internum and externum is absolute. (See text for details.)

Figure 7. Eudifferentiation. Cell specialization is achieved through communication and negotiated division of labor. At least two cells are required. The boundary remains fully permeable. Correspondence between internum and externum is fully enabled.
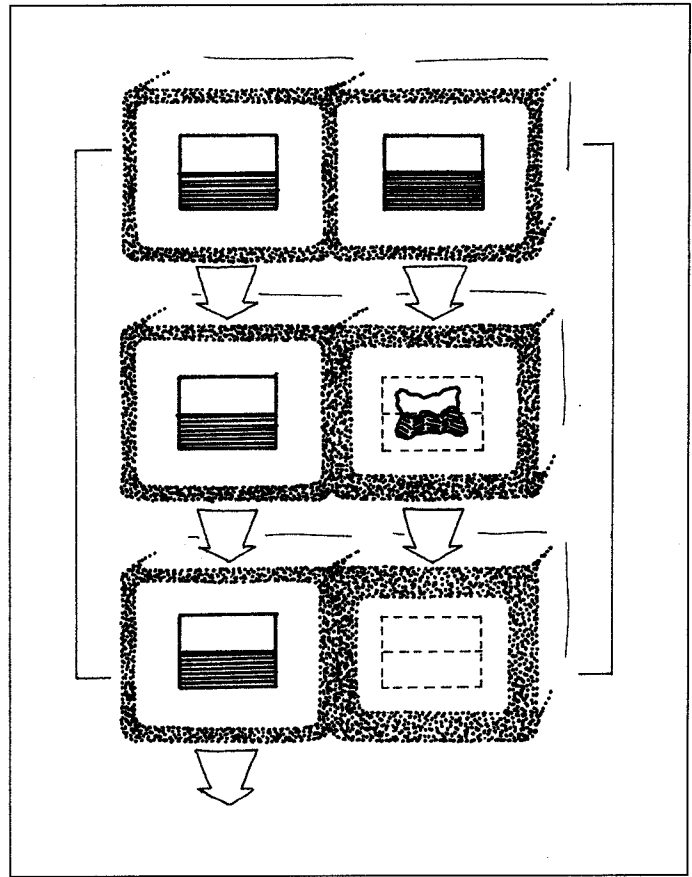
Figure 8. Teleodifferentiation (apoptosis). Contraction of cell function proceeds until cytoplasmic function ceases and the cell contents are consumed. The boundary ceases to exist. Internum and externum lose their meaning.

they become different specialized cells. Neither is dormant or dead, but the two function together in a complementary way to maintain a viable whole (Figure 7). This kind of differentiation is distinguished by the fact that it requires the participation of at least two cells.

• Teleodifferentiation. In this third type of differentiation, the cell contributes only its nonliving skeleton to the mature organism (Figure 8). This terminal self-sacrifice is a form of apoptosis or programmed cell death.

Clearly, these three examples represent quite distinct processes, and yet they are all commonly understood to qualify as legitimate examples of differentiation. In the case of autodifferentiation, for which the ready example is bacterial sporulation, the cell erects a barrier to exchange with the external world, selectively restricting the number of functions represented at the externum

and internum, and thereby restricting the flow of information and materials. This kind of differentiation, which is usually triggered by some environmental change, can, at least in principle, proceed autonomously, without input from neighboring cells.

At the other extreme, in the case of eudifferentiation, the two cells maintain open boundaries but relinquish functions to each other so that in the final differentiated state they are completely dependent on each other; neither maintains all of the functions necessary for viability, but together they complement one another and remain viable. Perhaps the best example of eudifferentiation is that quintessentially botanical example of differentiation, the phloem sieve tube–companion cell complex. At maturity, the sieve tube is a highly specialized, anucleate conductive cell that is closely attended by a normally nucleate companion cell, which presumably provides the nuclear function. The two cells have differ-

entiated from one another, and both are active metabolically, although in specialized ways. The sieve tube is dependent on the companion cell for nuclear products, and the companion cell is dependant on the sieve tube for nutrition. No impermeable wall is formed between them.

In the case of teleodifferentiation, a good example is that of a water-conducting cell, that is, a xylem vessel element. The xylem vessel element starts as a fully active metabolic cell, derived from cambium, but it subsequently undergoes a controlled process of growth and enlargement, elaborating a specialized and usually thick extracellular wall. It then dies before it achieves its final functional role as a tubular element in an extensive water-conducting system.

Focusing for a moment on the process of eudifferentiation, in which two identical cells gradually diverge in function, becoming specialized and therefore interdependent, it is apparent that the very first steps in this

process, beginning with two virtually identical postmitotic cells, must involve a mutually negotiated stepwise relinquishing of essential function. This negotiation means that the down-regulation of a particular vital function by one cell of a eudifferentiating pair must be accompanied by the up-regulation of that same function by its partner. Without such communication, differentiating cells risk being left without a full complement of necessary functions, and the viability of the individual cells will be compromised. Therefore, eudifferentiation requires that informational channels between the two cells remain open and that communication be ongoing. It further implies that eudifferentiation is analogous to a contractual negotiation: A series of agreements must be struck between the two differentiating cells, ensuring that neither one relinquishes vital functions in an untimely manner.

In the current literature on the topic of differentiation, the example of bacterial sporulation is frequently used as a model for eukaryotic differentiation (Losick 1995). However, this analogy would appear to be limited, because, like other forms of autodifferentiation, sporulation is achieved at the cost of communication with the external world, so that the way in which the necessities of Sands' Principle are met by a sporulating cell may be different from the way in which they would be met by a eudifferentiating cell. Although more complex forms of prokaryotic differentiation may be possible, it is clear that eudifferentiation, besides being intrinsically impossible in single-cell systems, requires more formal intercellular communication protocols and more sophisticated controls over cellular metabolism and intracellular resource management. Thus, eudifferentiation would appear to be characteristic of multicellular eukaryotic organisms, occurring to only a very limited extent in the prokaryotes.

The most spectacular example of intercellular dependency—namely, that between cellular endosymbionts (chloroplasts and mitochondria) and their host cells—is also strikingly different from eudifferentiation. Although these endosymbiotic relationships represent a high degree of interdependency and demonstrate true functional specialization, they are not capable of arising de novo from originally identical partners. In other words, the process by which this interdependency was established is not ongoing; instead, the basic relationship was established hundreds of millions of years ago and is maintained in the continued dependency between host cell and symbiont. The merits of eudifferentiation then become apparent in that the functional relationships necessary for the more complex types of biological development do not have to be carried forward from generation to generation in the form of a cytoplasmically inherited homunculus (i.e., the proplastid or promitochondrion) that contains the seeds of the differentiated cell types. The necessary relationships can instead arise epigenetically, providing that the differentiating partners are appropriately equipped and free to communicate with each other.

Understanding the cell is different from understanding what goes on inside the cell

In the case of terminal differentiation, or teleodifferentiation, the cell may or may not maintain open boundaries, but it commits all of its resources to the construction of a complex cell wall. In the process, the cell consumes itself, destroying the boundary. In this case, as with eudifferentiation and autodifferentiation, the end result is clearly a differentiated structure, but the process terminates the living entity itself, a sacrifice that stretches the meaning of the word differentiation in a new direction.

Most differentiating systems are a blend of the three basic types. In vessel element differentiation, for instance, there may be a period of eudifferentiation of the cambial derivatives, which is followed by a period of autodifferentiation that precedes teleodifferentiation. Many examples of eudifferentiation may also blend in an element of the exclusion that is characteristic of autodifferentiation, such as the differentiation of thick-walled idioblastic cells in plants. In general, most examples of eukaryotic differentiation show some elements of eudifferentiation, whereas differentiation in the prokaryotes tends to conform more strictly to the autodifferentiation model.

What distinguishes the three cellular processes that are included under the rubric of differentiation is that each is characterized by a particular behavior at the cell boundary. In autodifferentiation, the boundary itself changes and becomes increasingly impermeable, so that communication with the externum is reduced. Fewer and fewer functions correspond across the boundary, and the cell becomes insensitive to many environmental changes. In eudifferentiation, the boundary remains open and the cells remain viable, even though they have relinquished essential functions to each other. Individual cells become increasingly invested in their environments and neighbors. In teleodifferentiation, a period of auto- or eudifferentiation, either singly or in combination, is followed by a period during which the cell consumes itself, so that the boundary that defines internum and externum eventually ceases to exist and the living cell comes to an end, leaving only a nonliving extracellular skeleton in its place.

The significance of these distinctions lies in the fact that differences in the mechanics of differentiation imply differences in behavior and, ultimately, in the complexity and interconnectedness of the structures produced. Eudifferentiation may be a paradigm for all multicellular differentiation in that the controlled assignment of what would normally be internal cellular functions to external entities, whether they are neighboring cells or distant organs, must entail a similar sequence of "agreements" between internum and externum.

In all three forms of differentiation, the requirements of Sands' Principle must be met. Internum and externum must be reconciled at the cell surface, whatever the specialized nature of the cell, and at the same time essential functions must be provided for as long as the cell is alive.

One consequence of the notion that internally generated behaviors and externally generated stimuli are brought into correspondence at the cell boundary is that the cell represents an equilibrium between internum and externum. This notion distills the fundamental postulate deriving from Sands' Principle: *Internum and externum have equal roles in the determination of cellular behavior.*

Differentiation and the problem of resource management

A key question that confronts us in trying to understand cellular eudifferentiation is the nature of the relationship between cellular resource management and the negotiation of contracts between eudifferentiating cells, that is, between individual cell interna and their externa. In other words, what does "contractual negotiation" mean in terms of Sands' Principle and the allocation of cellular resources?

First, two cells must remain essentially identical as long as their externa remain identical. Because the cells are clonal, there is no internal command that can be invoked by one that will not necessarily be invoked simultaneously by the other. Consequently, the primary event in eudifferentiation must always be an external signal that affects the two cells differently, causing one to "see" an externum different from that seen by its companion. In plant tissues, such an external signal might be mechanical, resulting from differential growth stresses and transmitted from cell to cell through the continuous cell wall system, finally resolving itself as different stress mechanical environments at the locations of the two target cells.

One can visualize, however, that as soon as such a signal arrives at the pair of cells, a cascade of events occurs that results in a multiplier effect. The first cell will interpret and respond to the change in the externum with a change in its own internum. This change in the internum will be projected outward, where it will result in a change in the externum of the neighboring cell. The second cell will then respond with a change in its own internum,

which will then be resubmitted to the first cell. Each iteration of the process is akin to a proposal that is submitted, reviewed, and resubmitted. This incremental negotiation of mutually acceptable changes eventually cascades into the final metastable, interdependent, differentiated end state.

The net result of this process is that where interdependencies arise between cells due to eudifferentiation and functional specialization, different subroutines in effect become contractually assigned to separate cells. The term "hypercellular" can then be used to describe functions that are provided by one cell in excess of its own needs and that therefore come to be overrepresented at its surface. These hypercellular functions are therefore available for one or more neighbors. Similarly, the term "hypocellular" could be applied to cellular functions that have contracted to the point at which they are no longer capable of supporting even a single cell and must therefore be supplemented by outside sources and made available at the cell's externum. The terms hypercellular and hypocellular are the cellular analogues of biochemical up-regulation and down-regulation.

The logic of multicellularity. These seemingly necessary relationships can be used to construct a basic logic of multicellularity. For instance, it would follow from the above discussion that in a two-cell eudifferentiating system, when one cell has become hypocellular with regard to a particular function, the other cell must be hypercellular with respect to that same function for the pair to remain viable. Similarly, in a viable three-cell system in which the summed interna of any two cells are hypocellular for a given function, the makeup of the internum of the third can be inferred to be hypercellular with respect to that function. And so, too, in multicellular systems, tissue- and organ-wide deficiencies must in the end be reconciled at the level of individual cell interna and externa.
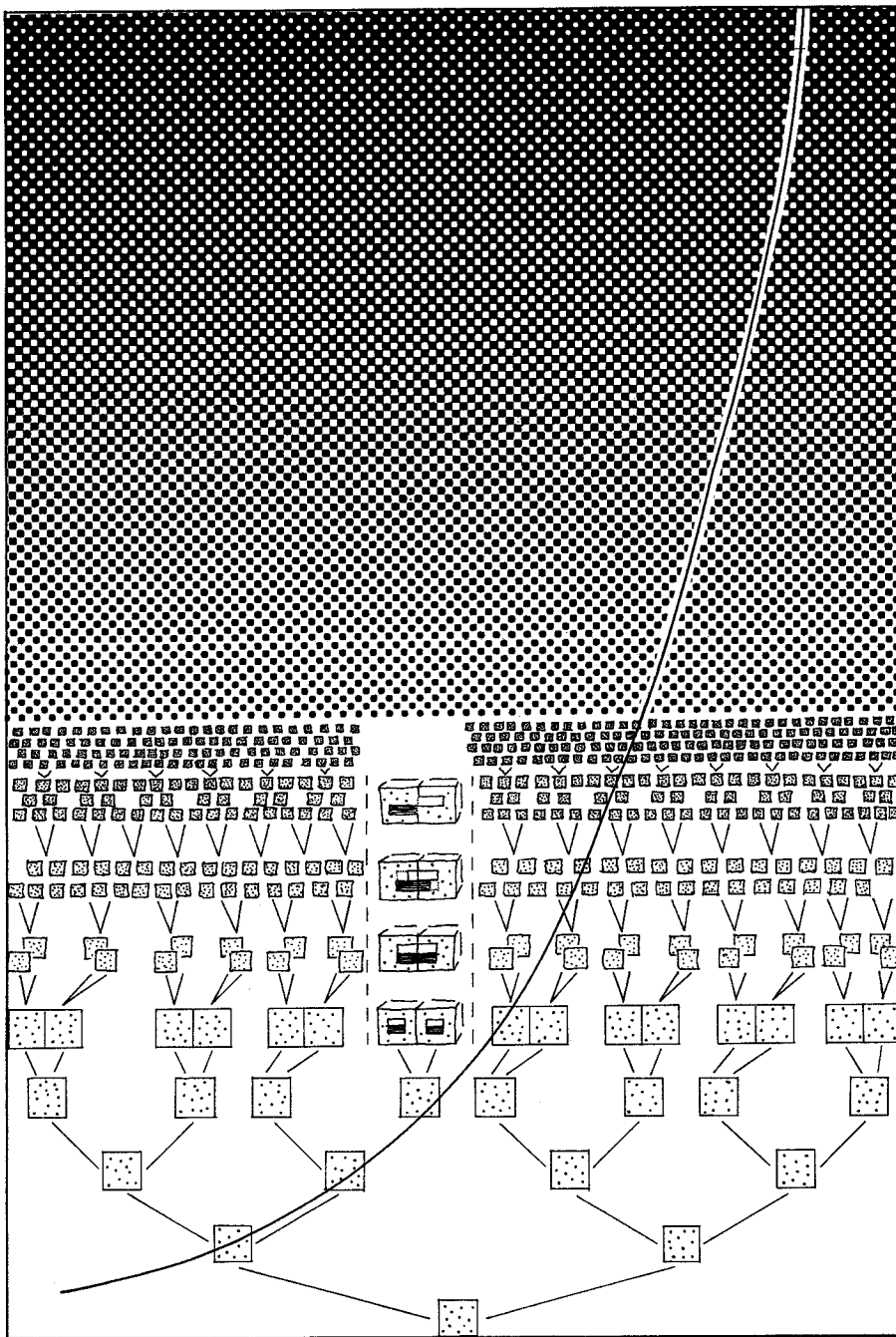
Finally, what is the relationship between growth (meaning the construction of new cytoplasmic components and cells) and differentiation? Clearly, in the case of teleodifferenti-

ation, further growth becomes impossible as the cell approaches its terminal end state and disappears. Similarly, in those examples of autodifferentiation in which the differentiated end state is a dormant cell or resistant spore, the process of differentiation eliminates any possibility of growth, not simply because the dormant cell cannot grow by virtue of physical restraint, but because fully enabled anabolic processes must be reflected in full correspondence across the cell boundary. What, then, of eudifferentiation and growth?

The growth dilemma. In general, for prokaryotes and eukaryotes alike, abundant substrate and favorable conditions will up-regulate metabolism and propel the cells into growth mode. But for eukaryotic cells, general metabolic up-regulation would appear to be intrinsically at odds with differentiation because, on the one hand, growth and division involves the replication of the entire machinery of the cell, and, on the other hand, eudifferentiation necessarily results in selective representation of some functions: hypocellular (down-regulated) in some cases, and hypercellular (up-regulated) in others.

How, then, can eudifferentiation occur in a substrate-rich environment? That is, how can contractual relationships between cells be arranged when the cells in question are committed to rapid logarithmic growth (Figure 9)? For a cell to engage in stepwise abdication of cellular functions to surrounding entities, the commitment to maximum reproductive capacity must be broken. Eudifferentiating cells must therefore find some way to slow anabolic metabolism and growth while maintaining open boundaries, even in a substrate-rich environment. This is not to say that cell growth and division and eudifferentiation are necessarily mutually exclusive. Procambial cells, for example, appear to be able to divide and differentiate at the same time. What do appear to be mutually exclusive, however, are fully enabled exponential growth and eudifferentiation.

Most eudifferentiating cells divide rarely, if at all, which raises the following question: Which came first,

Figure 9. Eudifferentiation and rapid exponential growth (the growth dilemma). Is there a basic conflict between the subtle demands of eudifferentiation and the necessities of rapid cell proliferation?

mechanism that causes incoming pathways to close. Third, energy and materials can be burned off by means of catabolic mechanisms that consume cellular resources without converting them into new protoplasm. This last mechanism brings up an interesting question: Did cellular motility (cyclosis) arise not as a means of locomotion but as a cellular mechanism for fine-tuning the cell's energy budget? Such a mechanism could allow the cell, even in times of substrate abundance, to free itself from the necessities of endless reproductive growth and begin to indulge in the delicate negotiations that must be part of eudifferentiation and that are the hallmark of eukaryotic growth.

The evolution of differentiation. It makes sense to place the differentiation process itself in an evolutionary context. In simple cells, we find the simplest kinds of differentiative changes. Plant cells afford the opportunity to easily observe eukaryotic differentiation because cell lineages are preserved in the patterns of tissues. In plants, then, in which cells maintain their relative positions to one another, we can still see the expression of eudifferentiation, in which the negotiation of individual cell differences has proceeded on a cell-by-cell basis. In animals, in which cell movement plays a major role in embryonic development, the role of individual bilateral or multilateral contract negotiations may be superseded by the ability of cells to place themselves in different environments by moving to different places. Furthermore, the whole question of functional specialization may be transferred to the tissue and organ level rather than proceeding on a cell-by-cell basis.

Any meaningful discussion of cellularity and its role in functional differentiation will eventually have to encompass a variety of solutions. But in plant cellular differentiation, it may be possible to study an intermediate stage in the evolution of differentiative mechanisms that lies somewhere between the simpler types of cellular change available to the prokaryotes and the more widely coordinated and complex changes available to animals.

the ability to down-regulate cellular metabolism in a substrate-rich environment or the ability to enter into complex intercellular separations of function? Part of my hypothesis is that the two are inseparably intertwined and that the key to eukaryotic eudifferentiation therefore lies in the ability to uncouple the linkage between substrate abundance and rapid exponential growth while maintaining the open boundary condition necessary for the development of true intercellular dependencies.

Apart from the universal cellular attribute of growth and division, eukaryotic cells would appear to have three ways to deal with excess energy in times of substrate abundance. First, energy can be sequestered as starch, glycogen, or other forms that remove it from the active energy budget of the cell. Second, energy can be rejected at the cell boundary by some

Conclusion

As to the notion of cellularity and the suggestion that it has only minimal significance in any general theory of plant development (Kaplan 1992), I propose that the seeming lack of relevance of individual cellular function to the overall pattern of organismal development is an artifact resulting from our incomplete understanding of the necessities of cell–cell interactions. Furthermore, this gap in our understanding of the contractual nature of cell interactions is in part a consequence of an inappropriate definition of the cell, which has led to a very limited view of the cell as a structural object—that is, as an encoded instruction set within a microscopic bag of enzymes that embodies a complex biochemical processor.

When we define the basic unit of life not as the individual histologically identifiable cell but as the boundary or "event surface"[2] that separates internum from externum (Figure 10), then the concept of the cell can expand or contract to include syncytial organisms, solitary unicells, differentiated cells within a multicellular domain, or, indeed, whole organs wherein individual cell boundaries have broken down, giving way to larger units of reactivity with their own boundaries. Such super cells of specialized function have interna that collectively negotiate a common relationship with the rest of the organism and externa that represent a genuine projection surface on which the interests of the rest of the organism are recorded. The obligate relationship between life and cellularity thus resides in the necessary requirement for a clearly defined event surface, rather than in the contents of the cell, the structural attributes of the extracellular matrix, or the size constraints that cellularity imposes on the internal workings of the cell.
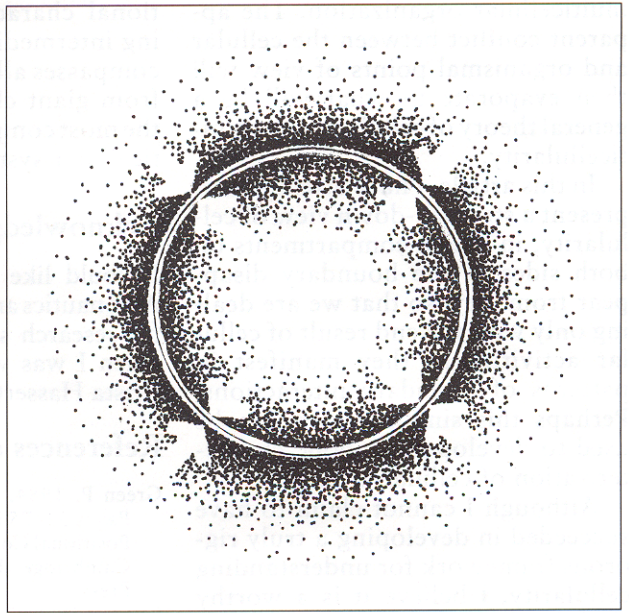
The power of Sands' Principle resides in its ability to reduce the entire universe of external influences to a

[2]The term "event surface" is meant to evoke the concept that the essential defining feature of the cell is not the machinery that is carried within it, but the boundary at which internal and external events are necessarily reconciled with each other.

Figure 10. The cell as an event surface. The irreducible element in cellularity is the boundary itself.

constellation of stimuli that are represented at the cell externum. Similarly, the complex world of the cell interior is represented at the cell surface by the limited constellation of factors that constitute the internum, whose spatial and temporal pattern can be interpreted as cellular responses or behaviors. Sands' Principle makes it possible to contemplate expressing the relationship of a cell to its environment in a single equation. Cellularity in all its manifestations then becomes a set of formal relationships between locally defined interna and externa.

It has been shown that properties such as shape (Green 1984), mechanical stress pattern (Lintilhac 1974), and kinematic flow (Silk and Erickson 1978), which emerge from whole organ structure, can be derived from a summation of individual cell characteristics. These properties may constitute a form of genuine organismal information. Thus, organismal control of the developmental process is real. These organismal factors may appear to have organ-wide organogenetic consequences that are independent of individual cell behavior, but they have their effect by means of coordinated chemical, mechanical, or electrical signals that appear in some form at individual cell externa. The broad similarity of the target cells, plus the multicellular nature of the eliciting stimulus, entrain whole regions of cells into similar behavior patterns.

Therefore, given the conceptual model and associated structure provided by a reconsideration of the nature of the cell and of cellularity, the cell is defined as a balanced relationship between an internum and an externum that complement each other across a common boundary. Increasingly complex multicellular differentiated structures are built up by codifying intercellular relationships in terms of contractual agreements that can, if necessary, be extended over large multicellular domains, eventually emerging as large-scale organismal influences that can again percolate down to the level of the single-cell externum, where they influence individual cell behavior.

Lewis Wolpert has raised the question of whether we are approaching the end of the major discovery era of developmental biology, which is to say, have all the basic principles of developmental biology been described? Given what we know in principle, then, is it possible to "compute" the developmental fate of an egg cell (Wolpert 1994)? I believe that there are whole areas of multicellular interaction for which no good theoretical framework exists on which to hang our extensive descriptive capabilities; therefore, we cannot at present contemplate "computing the egg." The underlying logic of cellularity is still a mystery, a fact that reveals itself in the nature of the questions that are still being raised about the role of the cell in development (Kaplan and Hagemann 1991, Kaplan 1992).

One of the immediate needs of developmental biologists is to formalize the relationship between what I have called internum and externum in terms of a basic equation of cellularity that can be built into a model of the most elemental two-cell differentiating systems and then extended into more complex models of

multicellular organization. The apparent conflict between the cellular and organismal points of view will then evaporate in what will be a general theory of cellularity and multicellularity.

In this article, I have attempted to present a stripped-down view of cellularity, in which compartments on both sides of the boundary disappear from view so that we are dealing only with the end result of cellular activities as they manifest in patterns of boundary interactions. Perhaps this simplification can be used to develop a symbolic characterization of cellular activities.

Although I cannot claim to have succeeded in developing a truly rigorous framework for understanding cellularity, I believe it is a worthy goal that holds the promise of relating all cell types in a precise taxonomy of relationships that integrates individual cell equilibria and higher-order boundary relationships throughout the organism to produce the emergent characteristics that we see as organismal properties. Thus, as developmental biologists we can envision a theory of cellularity that distinguishes prokaryotes and eukaryotes on the basis of their functional characteristics while resolving intermediate forms and that encompasses all eukaryotic organisms, from giant characean algal cells to the most complex differentiated multicellular systems.

Acknowledgments

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