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Interactions between Cells

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INTERACTIONS among cells are the means by which the cell community of the organism establishes and maintains its organizational harmony. They are so numerous and varied that it would take more space than is allotted here just to draw up a reasonably comprehensive list. Yet, knowledge about them is still very scanty. Fascinating progress has been made in the study of some of the biochemical and biophysical components of the living system. But knowledge seems to have grown the faster, the smaller the sample of the living system that was taken under investigation. The major advances were made down at the molecular level. The task of dealing with the larger cellular level, therefore, involves a re-entry into areas of uncertainty, and the course from the introductory article on cell dynamics (Weiss, p. 11) to the present article marks a full circle from relative ignorance through knowledge back to relative ignorance. The study of cells in interaction deflates complacent notions that all the major facets of cell life are truly understood even in principle.

"Interactions between cells" covers practically everything that is going on in organisms, and obviously this account must confine itself to a few crucial examples. There are essentially two ways for cells to interact: either a cell elaborates a diffusible substance which affects another cell at some distance, or a cell transmits an effect to another cell by direct contact. Since mediation by diffusible agents, as in the hormone system, is more widely studied and better understood than are the contact interactions, the emphasis here is on the latter. A more detailed account can be found in the author's recent review article on "Cell Contact."[1]

First, a few words on what is meant by "contact." It has been very easy to define contact between cells in terms of observations with the ordinary light microscope. If microscopically two cell borders came so close as to merge into a single line, there was contact, whereas a microscopic space in between signified lack of contact. Conversely, any interruption of the microscopic outline between two cells was interpreted as "protoplasmic continuity." But evidently, such questions of "contiguity" *vs* "continuity" between cells are merely questions of the resolving power of the instruments at hand. It is not surprising, therefore, that the introduction of electron microscopy has brought a marked change of outlook.

In the first place, electron microscopy has revealed a higher degree of organization at cell surfaces than previously assumed. As an example, one can cite the larval amphibian skin referred to in the introductory article (Weiss, p. 11). The underside of the epidermal cells, which rest on the basement membrane, is dotted at regular intervals with submicroscopic bodies, about 1200 A high, consisting each of two electron-dense round plates connected by a lighter neck.[2] The outer one of the plates forms part of the cell surface. This surface itself is separated from the underlying basement membrane by a gasket-like granulated film of a few hundred Ångströms thickness. The cell surface thus is actually a mosaic of patches of supramolecular order and different chemical and physical properties, which have been partly identified. This was done by applying various enzymes to fragments of live skin before they were fixed in osmium tetroxide and prepared for electron microscopy. In pancreatic lipase, the dark plates lose their osmiophilia, indicating that normally they have a high lipid content. In distilled water, the neck of these bodies swells and breaks, leaving unconnected double plates. Thus, the neck region is hydrophilic. Salivary amylase dissolves the film through which the epidermal cell is attached to the basement lamella, suggesting abundance of carbohydrate. It also erodes the parts of the cell surface between the dense bodies, but leaves the latter intact and protruding, thus identifying them as solid bodies.

Such observations demonstrate that it would be quite mistaken to consider a cell as being equal and uniform over its whole surface. Characteristically, this surface pattern is confined sharply to the portion of the cell that is in immediate apposition to the basement membrane, thus indicating a direct contact interaction between cell and substratum. This supposition is confirmed by experiments in which the contact between the two structures was first broken and then restored, as follows. When part of the skin is injured, the epidermal cells near the wound roll off. The dense bodies, which seem to serve as suckers to attach the cells to their substratum, become detached and are resorbed within a few days. They are re-formed during wound healing as the epidermal cells migrate over the defect, but are precisely confined to that fraction of cell surface now in fresh contact with the substratum. In other words, the cell has a mechanism for producing this specialized apparatus which responds to the interaction between cell surface and the underlying carbohydrate-rich film. As a result, an "induction" on the submicroscopic level occurs. The cell is induced along a geometrically and physically defined surface to display a specific fraction of its synthetic repertory. Other instances of contact induction are given later in this paper.

When two cells are in contact, the problem becomes more complicated. At the contact points between two

epidermal cells, single dark plates are present, the well-known nodes of Bizzozero. Electronmicroscopically, they show as a single dark plate in each of the contacting cells with a lighter space in between.[1] Odland[3] has recently scanned this region densitometrically in superior electron micrographs and has found an additional dark line in the center of the light interspace. This would indicate that the molecular array separating the two cell surfaces is not random, but has some degree of spatial order. It may be that the cell surfaces are linked by macromolecules normal to the surfaces of some 100 A in length, which is the order of width of the light space. Gaps of similar dimensions have been found between practically all cells that make intimate connections with each other, including synapses between nerve cells. It would seem best, therefore, to define two cells as being in contact, operationally speaking, when they are separated by a space whose contents are not subject to random perturbation. Depending on the dimensions, several factors might operate to limit perturbation of the interspace. For example, macromolecular compounds moving out of the cells may form bridges between organized parts and establish special submicroscopic attachments or interaction points between the adjoining cell surfaces. Evidence from tissue culture, obtained over a decade ago,[4] indicates that certain cells, and perhaps all cells, when left to their own devices, surround themselves with characteristic colloidal exudates, which must be taken into account when cell-to-cell relations are analyzed. Such surface coronas, extending for unknown distances into the cellular environment, might be major factors in immune reactions, cellular aggregations into colonies, phagocytosis of specific substances, selective associations among nerve fibers, and the like. It is equally possible that cell surfaces react with each other specifically without such mediators. A few examples are cited in the following.

In experiments on the development of nerve fibers, it has been found that fibers of the same type have a selective affinity to one another—motor fibers applying themselves to motor fibers, and sensory fibers to sensory fibers, and within each class, each subgroup to its corresponding type.[5] Only by virtue of such specific grouping is it possible for a surgeon, for instance, to expose the spinal cord and sever discriminately a bundle of pain fibers or of fibers for deep perception. Such fibers would not run in common bundles unless they had grown out that way, and since they do not develop all at the same time, the older fibers must have served as guides to latecomers of the same character.

The same principle applies, even more subtly, to the relations among the cells within the central nervous system on which the coordination of neural functions depends. Our current concern with the nervous system as a system centers mostly around such matters as geometric properties, electric parameters and time constants—length of interconnections within the network, number and distribution of branches, temporal characteristics of the individual units, synaptic resistances, etc. We generally ignore the fact that there is great biochemical diversity within the system far beyond the gross distinctions of cholinergic and adrenergic portions, which makes it work as something more than a monotonic network of conducting fibers. Developing nerve cells have highly selective discriminatory affinities by which they "recognize" each other and their surroundings. This introduction of the anthropomorphic term of "recognition" is not anything one need apologize for so long as physicists speak of electrons "seeing" each other. Recognition of one cell by another may be based on conforming charge distributions, on conforming molecular groupings, or on as yet wholly unsuspected mechanisms. The problem of explaining such recognition is of course encountered in many other biological phenomena, e.g., in enzyme-substrate relations and in antibody-antigen reactions. With a few notable exceptions,[6] affinity reactions among somatic cells, however, have received little attention and even less methodical study, even though there is ample evidence for the widespread occurrence of such selective behavior.

To cite a specific example, cells can "locate" their proper destinations in the body even if they are deprived of their customary routes for getting there. This has been shown[7] by letting embryonic cells of known destination be distributed at random through the blood stream of a host embryo. In order to be able to identify the injected cells, one chooses cells which carry a marker. We chose the precursor cells of pigment cells which, when introduced into nonpigmented breeds of chicks, would reveal their origin by synthesizing black melanin. It was found that after an injection of such cells into the blood stream, about 8% of the host chicks later carried scattered patches of black pigment cells in their feathers and skin. These pigment cells were always situated in the precise positions where such cells would have resided in the donor animals, and in no case was a pigment cell ever observed to have become lodged where pigment cells do not normally belong. One must conclude, therefore, that donor propigment cells had colonized only specified areas in the host embryos where such cells normally end up, which, in view of the random dissemination of the dissociated cells in the host body, implies the existence of a mechanism for highly selective localization. As few as one or two propigment cells, when arriving by chance at an appropriate site, "recognize" it and settle down to proliferate and differentiate into pigment cells. Cells that miss encountering within the embryo an environment favorable to their type fail to become lodged and to differentiate, and presumably are resorbed.

On the other hand, outside the embryo, on the yolk sac, where specific sites for embryonic cells are lacking, clumps of injected cells get stuck, and their fate led to a further significant extension of these observations. It was discovered[8] that, where random mixtures of em-

bryonic cells from a variety of sources (nerve, muscle, cartilage, glands, etc.) had become lodged on the yolk sac, they gave rise not to indiscriminately mixed structures, as might have been expected, but to quite harmoniously organized organ complexes. Some degree of self-sorting according to types must have taken place among these scrambled cells after they had become trapped.

Further conclusive evidence of "self-sorting" was found in tissue cultures in which random mixtures of suspensions of cells of different embryonic origins —for instance, cartilage and kidney cells—had been combined.[9] These cultures developed compound structures in which islands of pure cartilage were sharply demarcated from blocks of pure kidney tissue, indicating that cells had become re-associated like-to-like. Thus, even *in vitro* cells, which have acquired in their prior embryonic history some biochemical differential related to their subsequent development as either kidney cells or cartilage cells, can assort themselves according to type. Since the cells make contact only with their surfaces, one must assume that some property associated with differentiation into kidney cells or into cartilage cells has imparted type-specific markers to their surfaces for mutual recognition. But how such "recognition" leads to active sorting remains obscure.

How do mixed cell populations achieve this orderly reassortment? Do like cells "attract" each other? Or do they "recognize" each other only after chance encounters? A clue came first from some observations on selective wound healing after the grafting of various kinds of epithelia into skin gaps in the flanks of amphibian embryos.[10] The first coverage of a wound is effected by the migration of epithelial cells of the wound edge over the raw surface. When these advancing cells reach a graft, fusion of the two fronts occurs only if the graft contains an epithelium of a type which normally borders on skin epidermis. In that event, the advancing cells stop in their tracks, so to speak, merge into a uniform sheet with the graft, and no further proliferation occurs. Implants of skin, or of cornea or oral lining—which are normally continuous with skin—are accepted in this manner. But, when a fragment of lung or gall bladder or esophagus is implanted in a skin wound, the migrating skin epidermis is not halted on contact with those foreign-type cells. The epidermal edges glide over or under the graft and continue until they meet with the skin advancing from the opposite side.

Results of this kind have long been known in surgery and lead to the conclusion that, whether we have a plausible explanation for the phenomenon or not, cells of identical or conforming constitution (as epidermis, cornea, and oral lining) will recognize each other as akin and stay put; whereas cells of unlike character develop a reaction which will cause them to separate.

With these facts as background, we proceeded to study the contact reactions between different kinds of cells directly *in vitro*,[1] by taking phase-contrast time-lapse motion pictures of encounters among cultured cells.* If the cells that make contact are all of the same kind—all liver cells, for example—they aggregate and stay together. The free borders of roaming cells are in constant motion; but wherever two like cells touch each other, that portion of their surfaces becomes quiescent. The bond between them, however, is not static; there is no cement which sticks them together as in an immunological precipitin reaction. On the contrary, the cells continually glide over one another, constantly changing their positions relative to each other and, by the time others have joined them, their positions in the group.

On the other hand, if cells of two different types are cultured together (e.g., lung and liver or lung and kidney), the result is quite different. As the loose cells stray about, they collide at random. There is not the slightest indication that they would react to each other's presence unless or until their free borders touch. Neither do like cells "attract" each other, nor do unlike cells avoid each other. Mutual recognition and consequent discriminatory behavior are decidedly contact responses. All cells, whether alike or not, make primary contact indiscriminately. But, whereas like pairs thereafter draw closer together and remain joined, unlike pairs separate secondarily by reciprocal withdrawal of those parts of their borders that had been in fleeting touch. While the mechanism of identification undoubtedly resides in the surface, the interior of the cell seems to be engaged in the withdrawal reaction, giving the phenomenon the general appearance of a "reflex" response with a "sensory" and a "motor" component. The "reflex time" is of the order of 10^3 sec, varying both with the strangeness of the confronted cells and with their respective rates of motility. In conclusion, self-sorting of scrambled cell types results from chance collisions with matching combinations holding on to each other, whereas nonmatching ones do not last.

"Matching" combinations involve either cells of the same type or of complementary types, the latter being types that normally cooperate in the building and functional operation of complex organs. For instance, an active mutual adhesion between nerve processes and enveloping sheath cells has been demonstrated,[11] and our motion pictures reveal a similar marked tendency of macrophages to confine their excursions to within the borders of the large flattened lung cells with which they have been jointly explanted.

The discriminatory response is strictly cell-type specific, but it is not species specific. That is to say, cartilage cells of the chick will reject association with liver or kidney cells of the same chick, but they will combine readily with cartilage cells of a mouse. This fact, derived earlier from reaggregation experiments,[12] has now

* These moving pictures, made in collaboration with A. C. Taylor and A. Bock, were shown at the Study Program in Biophysical Science in conjunction with the lecture on which this article is based.

been proven visually by the motion pictures. On the other hand, the same cell type may undergo progressive alterations with age, so as to make more mature and less mature cells of the same strain less acceptable to each other than cells of the same age would be. Furthermore, there are signs that the differentials among cell types, which underly their discriminatory responses to each other, may be subject to gradations in accordance with their ontogenetic relationships.

The details of this principle still remain to be worked out. But what has emerged thus far is enough to force a substantial revision of former excessively static pictures of the organism as a fixed framework of parts shifted into predestined places by a rigidly prescribed system of tracks and schedules and then immured by fibrous cements. Although, grossly, this picture still holds, it gains much greater flexibility in detail from the realization that the eventual pattern of combination, association, and segregation among cell types in typically ordered arrays is not just passively arrived at, but is actively insured and guarded—and restored after disturbance—by a system of subtle mutual conformances and nonconformances with which the various cell types have been endowed as a corollary of their ontogenetic differentiation.

The principle of the self-linking of cells into matched groups by contact affinities and disaffinities has an important bearing on the explanation of the establishment and maintenance of order in the networks of the nervous system. The building up of central and peripheral nerve cables by the selective attachment of nerve fibers of a given type to others of like specificity has already been referred to in the foregoing. The same principle holds for interneuronal relations, as well as for the relations between neurons and their non-neural receptor and effector organs, on an even subtler scale. Since this is one of the most compelling, yet at the same time least recognized, instances of specificity and selectivity in cell-to-cell interactions, it is well to recapitulate briefly the relevant experiments, which I started almost forty years ago (see a recent review[13]) and which have more recently been amplified by my student, Sperry.[14]

During development, countless connections are established among individual neurons and between neurons and peripheral sense organs and muscles. The latitude inherent in the primary developmental mechanisms of neurogenesis[5] is so great that it would rule out any such microprecision in the details of the neuronal circuitry as is usually postulated as basis for coordinated functions. On the other hand, there is equally conclusive evidence to show that the nervous system does emerge from its embryonic phase with a large list of ready-made coordinated performances, which, since learning by trial and error could have played no part in their formation, must be explicable in terms of developmental interactions. The dilemma was solved by the demonstration of secondary processes which adjust the details within the gross primary system of connections to the unique arrangements of each individual specimen. Although nerves from the same central sources may in different individuals end up in different muscles, the muscles themselves then send a specifying influence back into the centers with the information on just what muscle of what name lies at the end of what line.

The test experiment consisted of transplanting a supernumerary muscle (or a whole set of limb muscles) near a normal limb and hitching it to a random branch of the local nerve supply. This amounted to "tapping" the communication network by inserting an extra receiver. What was observed then was that the transplanted muscle responded in the course of normal activities of the animal always at the precise time and with the same strength as the muscle bearing the same name in the normal limb. Thus, each muscle is called up, as it were, by the central system by its proper name, and if there are several muscles of the same name present in a common innervation district, they all respond simultaneously when the particular code is called. Since the test muscle was inserted arbitrarily, it is clear that it must have established its name-specific correspondences in the nerve centers secondarily. The same correspondence between periphery and centers was also confirmed for the sensory part of the system, first for proprioceptive[15] and tactile[16] sensations and later for the visual field.[14]

It all boils down to the following. Even though it is impossible to distinguish different skeletal muscles by present biochemical methods, the nervous system can tell them apart very well. Whatever the telling difference between muscles, it must be something that can make itself known in a retrograde manner over the motor nerve fiber in such a way that the central apparatus thereby gains exact information about its peripheral terminations. Motor fibers are initially blank and unspecified. They acquire specific identity only after they penetrate identified muscles at the periphery, and the same holds for sensory neurons in regard to their endings. Somehow, the acquired detailed specificity is then transmitted still further back from the primary to secondary neurons, and so on up the lines.

By this device, the neuronal population becomes progressively specialized into subunits whose member cells can henceforth regulate their own mutual relations by virtue of their acquired distinctive properties. Neurons of corresponding or complementary specificities thus become joined into cooperative systems. The proposition that this implies only linkage of a static morphological order all the way through the nerve centers[14] does not seem to go far enough if one is to explain either the aforementioned experimental results or the general problems of neural coordination.[13] But, if one adds the assumptions: that synaptic contact between neurons is merely an enabling, but not a decisive, condition for impulse transmission; further, that actual transmission requires specifically matched states of two apposed surfaces; and, finally, that the specificities

underlying this conformance are subject to modification by both peripheral and central influences; one comes closer to a satisfactory concept. The nervous system would then emerge as a vast system of resonance circuits, the elements of which would be linked by conforming molecular surface configurations, partly permanently, partly variably in response to changing central and peripheral influences.

From these remarks, it can readily be seen that compatibilities and incompatibilities along the boundaries between neurons are as significant as discriminatory devices as are the signs of surface "recognition" described earlier in this article for other cell types. Indeed, the direct demonstration of cell discrimination in the motion pictures should help to make the corresponding property of neurons acceptable, if not more palatable, to those who had hoped to be able to maintain their oversimplified faith in the essential identity of all neurons so long as they were faced only with the more indirect earlier evidence. In reopening the whole question of specificity in the nervous system, which of late has been lying dormant, our observations on cell encounters in tissue culture thus assume added significance, as they also open the way to a more direct practical study of the nature of the specificities concerned.

The reference to the progressive diversification within nerve-cell populations points logically to the more elementary question of how any primitive cell types, including neurons, acquire their distinguishing characteristics in the first place. To discuss the problem of divergent differentiation would go far beyond the scope of this article. There is one aspect, however, that fits into the context. Differentiation occurs essentially by dichotomies in the courses of transformation of cells with basically identical physical and chemical endowments.[17] Any cell strain is, by virtue of such endowments, initially capable of effecting a limited variety of qualitatively different reactions. Every step of differentiation implies that from that multiple repertory one definite course has become activated in some members of the group, and an alternative course in the other members, the two courses being mutually exclusive. Sooner or later, the different reactions lead to manifest diversity. Development is composed of long series of such steps. Present evidence is that each step has its own mode of triggering mechanism, and that, contrary to earlier illusions, there is no single master agent that could be held generally accountable for the various and successive dichotomous changes. Formally, however, one can distinguish two classes—one in which the differentiating activity plays entirely within the bounds of a group of similar cells, referable perhaps to differential interactions among the members of the group depending on their relative positions; and another in which the reaction of a given cell group is decisively influenced by an extraneous cell group.

This second class is usually termed "induction"; again, different steps of "inductive" influences need have little in common but the name. Some of them operate over distances, others only between adjacent tissues. Evidently, these latter raise the issue of whether true contact interactions are involved. The answer seems to be that in some instances and for certain steps of differentiation, intimate contact between the interacting cells is essential, whereas, in other cases, such direct contact is dispensable, the interaction being mediated by diffusible substances.

Some cases in which direct contact is necessary may be cited as examples. When devitalized (frozen-dried and rehydrated) cartilage is transplanted into the vicinity of a limb bone in amphibian larvae, the implant can induce the formation of new cartilage in contact with its surface.[1] Thus, competent living host cells build on cartilage to the dead cartilage model as bees would build on new honeycomb to an artificial wax honeycomb presented to them. This is a particularly interesting case, because the bodies of the cells in the implant cannot have been the inducing agents directly, as they are enclosed and insulated in the cartilaginous matrix; therefore, the inductive stimulus to surrounding host cells must have originated in the exposed surface of that matrix. Another set of experiments showed the same thing for bone.[1] A frozen-dried and rehydrated metatarsal bone of a rat, inserted into the leg of a host rat, induced there new bone, including new bone marrow, in contact with the old bone. That contact is essential has been confirmed from other sources.[18] Such observations support the conclusion that extracellular materials may play important roles in certain inductive interactions.[19]

The next case is of special interest to students of collagen. The stroma of the cornea consists of layers of collagen in a characteristic regular arrangement. When frozen-dried cornea was transplanted into a corneal defect in rabbits, the grafted stroma as such persisted for many months. In addition, however, it induced along its inner side the formation of several new layers of typical stroma.[20] Thus, the architecture of the dead stroma matrix has in some fashion been transmitted to the induced layers, so that they assumed the characteristic pattern of collagenous corneal lamellae. This result again proves that not only cells but cellular products likewise can influence other cells inductively.

The intimacy of submicroscopic cell contact, in the sense of the introductory remarks, which may be required for "contact inductions" has not yet been clarified. One of the few clues is the fact that, during the period of inductive interaction between eye cup and prospective lens epithelium, the attachment between the interacting cell layers is so firm as to resist mechanical separation.[21] But, it is still undecided whether the specific transmission across the cell borders is simply an orienting or sorting influence on pre-existing molecular populations[22] or whether it involves the actual passage of substance,[23] perhaps prepared by molecular reorienta-

tion.[1] There is a vast field here for exact studies on the relations between physical configuration and chemical activities. These relations are bound to remain in obscurity so long as one focuses attention on those cell-to-cell influences that are mediated not by contact, but by remote control through diffusible agents. The latter, although equally real, can tell only part of the story of cellular interaction.

In summing up, to state that all of the specific interactions among cells exemplified in this article are based on specific properties of the interacting cells is a truism. But, it explains why so little is known about the molecular phenomena governing cell-to-cell relations. There just has not been enough preoccupation with the molecular basis of cellular specificity. Unquestionably, cell "recognition" and selective response must eventually be reduced to terms of properties of molecules and molecular populations. But, so far, there has been very little tangible progress in that direction. There have been a few hypothetical suggestions to explain cell-to-cell conformances, none of them quite tenable in the light of recent observations. I had proposed[24,25] that some sort of steric fitting (e.g., by corresponding charge distributions) between complementary molecules might produce bonds or linkages between like cells, whereas unlike cells without conforming molecules in their surfaces to interlock could establish no connections. Yet, this supposition is now clearly contradicted by the fact that like cells, while remaining together, are not fastened but move continuously around each other. This leaves us for the time being without substantial explanation of the phenomena of selective aggregation as shown in the films.

The only thing that seems clear is that these phenomena point to the same general area of specificity that covers immune reactions,[26] enzyme-substrate interactions, pairing of chromosomes, fertilization, parasitic infection, and phagocytosis. The latter clearly involves selective uptake of particles of suitable molecular surface organization. The problem is no different from that met in cell-to-cell encounters, except for the great disproportion of size between the members of the pair in phagocytosis. Presumably, the selective ingestion of macromolecules belongs in here, too, with the discrepancy of size even more pronounced. The opposite extreme is found in a cell which spreads out selectively over a large body of proper substratum, where the cell is very small in comparison to the partner which it tries to engulf. So, from phagocytosis and the uptake of macromolecules, through cell-to-cell contacts with specific "recognitions," up to the problem of selective adhesion of a cell to its substratum, one deals with a continuous spectrum of problems of the same nature.

This very fact holds promise of progress, as advances in any one sector of that broad area will shed light on other sectors. On the other hand, cleverly getting around the acknowledgment of specificity in any one sector, whether by theoretical constructs or by unrealistic models, will not strip the other sectors of their aspect of specificity, and, hence, will not relieve the intellectual discomfort engendered by our inability to squeeze the broad subject of specificity into the limited conceptual framework which we have erected from the study of fragmentary vital phenomena lacking that aspect. Specificity, as a real and basic control mechanism of cell behavior, can no longer be relegated to a corner, but must be placed in a central position in cellular and molecular biology. The less that is known about it, the greater is the challenge. If there has been some dodging in the past, it was because of some concealed hope that the whole thing might yet in the end turn out to have been an illusion born of inadequate penetration. Exactly the opposite has happened. The more penetrating the analysis, the more cogent has the evidence of specificity become; witness the motion pictures of cell discrimination. There seems little doubt that once the reality and universality of the problem are generally acknowledged, and the promising techniques at our disposal for its disciplined study are recognized, progress can be rapid. But there is even less doubt that, if the existence of the problem continues to be widely ignored, or even denied, some of the major clues to the understanding of living systems will remain missing.

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