The New
ATLANTIS
A Journal of Technology & Society

The Unbearable Wholeness of Beings

Steve Talbott

***Editor's Note**: This is the second in a set of essays by Mr. Talbott explaining the significance of a revolution in genetics and molecular biology. The first installment, "Getting Over the Code Delusion," which appeared in our Summer 2010 issue, sought to puncture some of the familiar dogmas about DNA as rigidly encoded destiny.*

If you try to describe the living processes of the cell in a rather more living language than is typically found in the literature of molecular biology—if you resort to a language reflecting the artfulness and grace, the well-coordinated rhythms, and the striking choreography of phenomena such as gene expression, signaling cascades, and mitotic cell division—you will almost certainly hear mutterings about your flirtation with "spooky, mysterious, nonphysical forces." You can expect to hear yourself labeled a "mystic" or—there is hardly any viler epithet within biology today—a "vitalist."

This charge reflects a certain longstanding sensitivity among biologists—one that deserves to be taken seriously. It was recently given very thoughtful and respectful expression by a first-rank molecular biologist in response to a draft book chapter I had sent him. After describing my views as "very interesting, provocative, and necessary," and before offering his support for much of what I had to say, he voiced this concern: "You very explicitly dispense with vitalism. Nevertheless, your piece is permeated by an atmosphere that says 'There *is* something special about living things.'"

So I believe there is. Animals and plants are a long way from rocks and clouds, and also from automobiles and computers. The need to point this out today is one of the startling aspects of the current scientific landscape. It is true that the concept of "vitalism" has been problematic in the history of biology, but no less so than "mechanism." The two problems are in fact devilishly intertwined. We will never get straight about vitalism if we do not also get straight about mechanism. And until we sort through

***Steve Talbott**, a* New Atlantis *contributing editor, is a senior researcher at the Nature Institute and the editor of* NetFuture, *an online newsletter about science, technology, and human responsibility (netfuture.org). He is the coauthor, most recently, of* Beyond Biotechnology: The Barren Promise of Genetic Engineering *(University Press of Kentucky, 2008).*

the associated confusions, we have little hope of meaningful conversation about many of the perplexities vexing biologists today.

We will see, however, that the shoe is really on the other foot: it is the conventional literature of biology—and above all the literature of molecular biology—that is steeped in a kind of mysticism now blocking progress. What is required is a much greater rigor in the use of scientific terminology. And let me add that, in the interest of such rigor, I will avoid as far as possible the use of devil-terms such as "vitalism" and "reductionism"—words that philosophers of biology today generally reject as too ideologically burdened to be of much use. Better to say what one means directly than to lob undiscriminating verbal explosives onto the field of conversation.

Here, then, is my question: Are you and I machines? Are we analyzable without remainder into a collection of mechanisms whose operation can be fully explained by the causal operation of physical and chemical laws, starting from the parts and proceeding to the whole? It might seem so, judging from the insistent testimony of those whose work is to understand life.

There is little doubt about the biologist's declared obsession with mechanisms of every sort—"genetic mechanisms," "epigenetic mechanisms," "regulatory mechanisms," "signaling mechanisms," "oncogenic mechanisms," "immune mechanisms," "circadian clock mechanisms," "DNA repair mechanisms," "RNA splicing mechanisms," and even "molecular mechanisms of plasticity." The single phrase "genetic mechanism" now yields over 25,000 hits in Google Scholar and the count seems to be rising by hundreds per month. But no cellular entity or process is exempt; everything has been or will be baptized a "mechanism." In an informal analysis of technical papers I've collected, I found an average of 7.5 uses of *mechanism* per article, with the number in a single article varying from 1 to 32. This is not even counting cognate forms such as *mechanistic* and *machine*.

The odd thing is that I have yet to find a single technical paper in molecular biology whose author thought it necessary to define *mechanism* or any of the related terms. If the meaning is supposed to be obvious, then presumably we should read the words in a straightforward and concrete way—as indeed seems to be required in the case of *molecular machines*, which unashamedly projects the human machine shop onto the molecular level. Other usages, however—such as *causal mechanism* and *mechanistic explanation*—evidently convey little more than an idea of physical lawfulness or causation, as when one research team refers to "mechanistic insights into maintenance of cell phenotype through successive cell divisions."[1] Whatever the implicit definitions may turn out to be, it is

plain that the intertwined notions of mechanism and physical law intimately coinhabit the minds of biologists today and are held to be keys for understanding organisms.

But here is the greater curiosity: the same biologists rely on an equally pervasive and utterly different terminology—so different and yet so seemingly inescapable as to demand, from any thoughtful researcher, some sort of reconciliation with the language of mechanism.

What Changes at Death?

Anyone whose pet dog has died knows the difference between a living animal and a dead one. Biologists surely know this, too, although (strangely enough!) the difference between life and death does not often figure explicitly in the technical literature presuming to characterize living creatures. You might even think there is something slightly embarrassing about the subject. But, looked at in the right way, the biological literature nevertheless tells us what the biologist knows about the matter. And it is a great deal, even if he would prefer not to acknowledge it.

Think first of a living dog, then of a decomposing corpse. At the moment of death, all the living processes normally studied by the biologist rapidly disintegrate. The corpse remains subject to the same laws of physics and chemistry as the live dog, but now, with the cessation of life, we see those laws strictly in their own terms, without anything the life scientist is distinctively concerned about. The dramatic change in his descriptive language as he moves between the living and the dead tells us just about everything we need to know.

No biologist who had been speaking of the *behavior* of the living dog will now speak in the same way of the corpse's "behavior." Nor will he refer to certain physical changes in the corpse as *reflexes*, just as he will never mention the corpse's *responses* to *stimuli*, or the *functions* of its organs, or the processes of *development* being undergone by the decomposing tissues.

Virtually the same collection of molecules exists in the canine cells during the moments immediately before and after death. But after the fateful transition no one will any longer think of genes as being *regulated*, nor will anyone refer to *normal* or *proper* chromosome functioning. No molecules will be said to *guide* other molecules to specific *targets*, and no molecules will be carrying *signals*, which is just as well because there will be no structures *recognizing* signals. *Code*, *information*, and *communication*, in their biological sense, will have disappeared from the scientist's vocabulary.

The corpse will not produce *errors* in chromosome replication or in any other processes, and neither will it *attempt* error *correction* or the *repair* of damaged parts. More generally, the ideas of *injury* and *healing* will be absent. Molecules will not *recruit* other molecules in order to *achieve* particular *tasks*. No structures will *inherit* features from parent structures in the way that daughter cells inherit traits or tendencies from their parents, and no one will cite the *plasticity* or *context-dependence* of the corpse's *adaptation* to its environment.

It is a worthwhile exercise: try to think in all these ways about the corpse. You will immediately come up against your experience of the distinction between the dog and its remains, between a strictly physical process and a living performance. Nor need you be ashamed of your experience; the most disciplined biologist, whatever his theoretical inclinations, is leaning very much on the same meanings and distinctions you apprehend. Words such as those cited above, after all, are woven into the decisive explanatory matrix of virtually every contemporary paper in molecular biology—but not in papers dealing with the physical sciences.

Sometimes, in fact, the biologist's language may reach beyond your own intuitions, as when two researchers say that we might gain "insights into the *'thought'* processes of a cell" (emphases added here and in the following). The same two researchers describe signaling networks as the "*perceptual* components of a cell," responsible for "*observing* current conditions and making *decisions* about the *appropriate* use of resources—ultimately by *regulating* cellular *behavior*."[2] Another excellent case in point is the geneticist Barbara McClintock's 1983 Nobel Prize address, in which she surmised that "some *sensing* mechanism must be present…to *alert* the cell to imminent danger." In the future we should try to "determine the extent of *knowledge* the cell has of itself and how it utilizes this knowledge in a *'thoughtful'* manner when challenged."[3]

But even without references to thought and perception, biologists cannot open their mouths without employing a language of recognition and response, of intention and directed activity, of meaningful information and timely communication, of aberrant actions and corrective reactions, of healthy development leading to self-realization or ill health leading to death. Yes, all this language sits side by side with the familiar appeals to *causal mechanisms*. But does it sit comfortably?

We must explore the use of this special language of life—this decidedly non-corpselike language—much further before we can answer that question.

Some Views of the Living Organism

On its face, the language noted above—*recognize*, *respond*, *function*, *adapt*, *regulate*, and so on—suggests that something is going on over and above a physically lawful performance. In employing the conventional terminology, we describe a kind of directed choreography—a performance whose nature and intent is sufficiently clear for us to judge when *errors* occur or *injury* supervenes. (Rocks and clouds do not commit errors or suffer injury.) This implies that we are comfortable making qualitative and aesthetic judgments about *health*, and can distinguish between coherent and errant *meaning* in the various informative exchanges continually taking place throughout cell and organism.

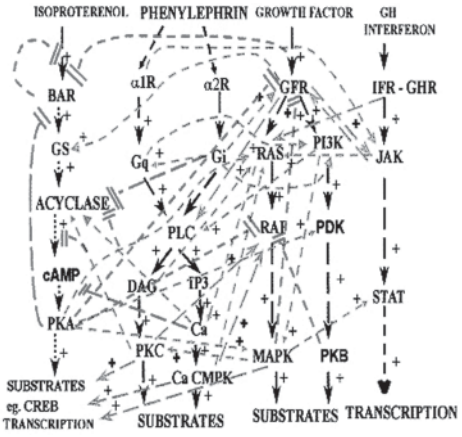
We speak, in other words, as though the performer (whatever subject we intend for verbs such as "regulate" and "adapt") were a real entity or being, capable of signaling or otherwise communicating its own needs and designs, able to make sense of the signals coming from its environment, and, through it all, striving to maintain its own distinct, healthy identity.

But it's not just isolated words and phrases that point to the organism as something more than a collection of physically lawful mechanisms. The larger narratives to which these words lend their meanings are narratives of life, not of carcasses—and much less (as we will see) of machines. Is there any subdiscipline of biology today where research has been reducing cellular processes to a more clearly defined set of causal mechanisms instead of rendering them more ambiguous, more intentional, more plastic and context-dependent, and less mechanical?

We saw in the previous essay in this series that the chromosome, far from being a kind of fixed, crystalline structure, "is a plastic polymorphic dynamic elastic resilient flexible nucleoprotein complex,"[4] and its living expression is fully as central to its meaning as the "coded" genetic sequence. But the chromosome is only one element of the cell. Here are a few of the countless other developing stories in molecular biology that speak of organic activity fully as dramatic as the dance of chromosomes.

Signaling Pathways. Signaling pathways are vital means of communication within and between cells. Such pathways are coherent sequences of molecular interactions by which an initial encounter—say, the binding of a hormone to a cell membrane receptor—leads to a more or less defined result, or group of results, "downstream." One result, for example, might be the activation of a set of genes.

In the conventional machine model of the organism, signaling pathways were straightforward, with a clear-cut input at the start of the pathway leading to an equally clear-cut output at the end. Not so today, as a team of molecular biologists at the Free University of Brussels found out when they looked at how these pathways interact or "cross-talk" with each other. Tabulating the cross-signalings between just four such pathways yielded what they called a "horror graph" (right), and quickly it began to look as though "everything does everything to everything."[5]



Graph courtesy of Jacques E. Dumont. From "Crosstalk and Specificity in Signalling," *Cellular Signalling* 13 (2001): 458.

Alternatively, as another research group has put it, we see a "collaborative" process that can be "pictured as a table around which decision-makers debate a question and respond collectively to information put to them."[6]

Even considering a single membrane receptor bound by a hormonal or other signal, you can find yourself looking, conservatively, at some two billion possible states, depending on how that receptor is modified by its interactions with other molecules. There is no simple binary rule distinguishing activated from deactivated receptors, as once was believed. In reality, as a team from the University of Connecticut Health Center recently explained in the *Journal of Biology*, "the activated receptor looks less like a machine and more like a…probability cloud of an almost infinite number of possible states, each of which may differ in its biological activity."[7]

Our problem lies in adequately imagining the reality. When a single protein can combine with several hundred different modifier molecules, leading to practically infinite combinatorial possibilities, and when that protein itself is an infinitesimal point in the vast heaving and churning molecular sea of continual exchange that is the cell, and when the cell is one instance of maybe 100 trillion cells of hundreds of different types in the human body, from muscle to bone, from liver to brain, from blood to retina—well, it's understandable that many researchers prefer not to stare too long at the larger picture. Nevertheless, we should keep in mind that the collaborative process mentioned above involves not just one table with

"negotiators" gathered around it, but countless tables with countless participants, and with messages flying back and forth in countless patterns as countless "decisions" are made in a manner somehow subordinated to the unity and multidimensioned interests of the organism as a whole.

In other words, not only are the elements of an individual signaling pathway extremely flexible and adaptive; the individual pathway itself, once thought of as discrete and well-defined, does not really exist—certainly not as a separate "mechanism." Researchers now speak of the "multi-functionality" of signaling nodes, pointing out that signaling networks have "ways of passing physiologically relevant stimulus information through shared channels."[8] More generally, "We tend to talk about pathways and processes as if they are discrete compartments of biology," write geneticists Emmanouil Dermitzakis and Andrew Clark. "But genes and their products contribute to a network of interactions"—and these interactive networks "differ radically among tissues."[9]

Whenever we imagine a biological process aimed at achieving some particular result, we need to keep in mind that every element in that process is likely playing a role in an indeterminate number of other significant, and seemingly goal-directed, activities. The mystery in all this does not lie primarily in isolated "mechanisms" of interaction; the question, rather, is why things don't fall completely apart—as they do, in fact, at the moment of death. What power holds off that moment—precisely for a *life*time, and not a moment longer?

Demise of Lock-and-Key Proteins. Quite apart from its wider context of exchange and interaction, the protein molecule itself is an entire universe of plastic form and possibility. It reminds us that messages do not fly back and forth as disembodied abstractions; they move as dynamically sculptured bodies of force and energy. Their meanings are mimed or gestured—not translated into or reduced to a kind of expressionless Morse code.

According to the old story of the machine-organism, a protein-coding DNA sequence, or gene, not only specifies an exact messenger RNA (mRNA) sequence, but the mRNA in turn specifies an exact amino acid sequence in the resulting protein, which finally folds into a fixed and predestined shape. These proteins then carry out their functions by neatly engaging with each other, snapping into place like perfectly matched puzzle pieces or keys in locks. "There is a sense," wrote Richard Dawkins in his 1986 book *The Blind Watchmaker*, "in which the three-dimensional coiled shape of a protein is determined by the one-dimensional sequence of code symbols in

the DNA." Further, "the whole translation, from strictly sequential DNA ROM [read-only memory] to precisely invariant three-dimensional protein shape, is a remarkable feat of digital information technology."[10]

This is as forthright a statement as ever there was of the "code delusion," and we now know how great a misconception it was (a misconception upon which, in Dawkins's case, his entire metaphysical-religious-scientific scheme of the "selfish gene" was erected). But the truth of the gene and protein looks quite different from this computerized ideal. Through alternative splicing, one gene can produce up to thousands of protein variants, while unlimited additional possibilities arise from RNA editing, RNA cleavage, translational regulation, and post-translational modifications. ("Translation" refers to the process by which an mRNA molecule, along with a large supporting cast, yields a protein.) As for the finally achieved protein, it need not be anything like the rigid, inflexible mechanism with a single, well-defined structure imagined by Dawkins. Proteins are the true shape-changers of the cell, responding and adapting to an ever-varying context—so much so that the "same" proteins with the same amino acid sequences can, in different environments, "be viewed as totally different molecules," with distinct physical and chemical properties.[11]

Nor is it the case that proteins must choose in a neatly digital fashion between discrete conformations. In contrast to the old "rigid-body" view, researchers now refer to "fluid-like"[12] and "surface-molten"[13] protein structures. Even more radical has been the discovery that many proteins never do fold into a particular shape, but rather remain unstructured or "disordered." In mammals, about 75 percent of signaling proteins and half of *all* proteins are thought to contain long, disordered regions, while about 25 percent of all proteins are predicted to be "fully disordered."[14] Many of these intrinsically unstructured proteins are involved in regulatory processes, and are often at the center of large protein interaction networks.[15]

Fluid, "living" molecules do not lend themselves to the analogy with mechanisms, which may explain why the mistaken idea of precisely articulated, folded parts was so persistent, and why the recognition of unstructured proteins has been so late coming. Indeed, this recognition has hardly yet dawned on the biological community as a whole, leading to this lament at a conference on "bioinformatics and bioengineering" at Harvard Medical School:

> Experimentalists have been providing evidence over many decades that some proteins lack fixed structure or are disordered (or unfolded) under physiological conditions. In addition, experimentalists are also

> showing that, for many proteins, their functions depend on the unstructured rather than structured state; such results are in marked contrast to the greater than hundred-year-old views such as the lock-and-key hypothesis. Despite extensive data on many important examples, including disease-associated proteins, the importance of disorder for protein function has been largely ignored. Indeed, to our knowledge, current biochemistry books don't present even one acknowledged example of a disorder-dependent function, even though some reports of disorder-dependent functions are more than fifty years old.[16]

A continuing mechanistic bias is evident even in the negative terms "disordered" and "unstructured." The loose, shifting structure of a protein need be no more disordered than the graceful, swirling currents of a river or the movements of a ballet dancer. Given what these proteins harmoniously participate in (among other things, the movements of a ballet dancer), it seems strange to assume that their performance is anything *less* than graceful and artistic.

The Organism Reveals Itself Through Many Complementary Viewpoints. The living, non-mechanical qualities of the organism are evidenced not only in flexible, collaborative signaling and the plastic dynamism of proteins, but also in the organic unity of the whole, whereby every aspect of the organization is qualified by all the other aspects. There is a mutual interpenetration of processes making it impossible to offer simple chains of causal explanation. The result is that in order to understand the whole we have to take up many different and partial viewpoints—something that was hardly necessary so long as the one-dimensional, machine-like DNA code provided the single and undisputed basis for understanding.

There is, for example, the "ribonome"—the entire collection of RNA molecules along with the diverse proteins that associate with them. Australian researcher John Mattick argues that RNA is the true "computational engine of the cell."[17] This "engine" includes numerous large and small RNAs whose functions are the result, not simply of their transcription from DNA, but of their elaborate processing and restructuring within nucleus and cytoplasm. RNA in general

> is known or strongly implicated to be involved in the regulation of gene expression (both protein-coding and noncoding) at all levels in animals, creating extraordinarily complex hierarchies of interacting controls. This includes chromatin modification and associated epigenetic memory, transcription, alternative splicing, RNA modification, RNA

> editing, mRNA translation, RNA stability, and cellular signal transduction and trafficking pathways.[18]

It is true that RNA seems to have its hand in just about everything. And yet, others think of signaling pathways as the decisive, overall integrators: "It is becoming increasingly obvious that cellular signaling pathways control gene expression programs at multiple levels, from transcription through RNA processing and finally protein production."[19] For still others, chromatin in general and the nucleosome in particular provide the clearest vantage point. As structured by nucleosomes, chromatin "[tells] the story of the genome in a more compact way without skipping the important features. Well defined, predictive chromatin signatures offer an elegant framework to comprehensively map all the functional elements in the human genome."[20]

There are further possibilities as well, such as the complex regulation of protein translation.[21] Even the elaborately articulated, information-rich, and too often overlooked membrane architecture of the cell can be seen as playing a vital role in organizing and structuring the activity of the cell:

> Cellular organization in general and membrane-mediated compartmentalization in particular are constitutive of the biological "meaning" of any newly synthesized protein (and thus gene), which is either properly targeted within the context of cellular compartmentalization or quickly condemned to rapid destruction (or cellular "mischief"). At the level of the empirical materiality of real cells, genes "show up" as indeterminate resources. . . . If cellular membrane organization is ever lost, neither "all the king's horses and all the king's men" *nor* any amount of DNA could put it back together again.[22]

Perhaps it is the case that, regardless of the vantage from which we look at the organism, deep inspection will yield a view onto the whole, just as any sentence of a profound and unified text, or any scene of a Greek tragedy, when penetrated deeply enough, opens out onto the meaning of the whole. At the same time, no single view yields a complete or fully adequate description of the whole. There is no one "correct" focus for the biologist; we discover instead numerous complementary perspectives.

The Organism Is Not a Machine

We can now return to biologists' preoccupation with mechanistic terminology. Given the contrast between the ubiquitous appeal to mechanisms in the technical literature on the one hand, and the actual qualities of organisms revealed by the language of biological description on the

other, the lack of forthrightness by researchers regarding what they mean by "mechanism" is remarkable. After all, there is no obvious similarity between a sewing machine or clock or any other machine and, say, a twisting, gesturing chromosome—or, for that matter, a cat stalking a mouse.

Here is another way to think of the impropriety of the language of mechanism to describe life. The typical living cell is 75-80 percent water. Its primary activities are *flows*. Even the parts we have been taught (by photographs and textbook drawings) to take as fixed structures are in fact caught up in flows. They themselves *are* in one degree or another flows. For example, the filamentous cytoskeleton that helps give the cell a degree of rigidity and maintain its form "is not a fixed structure whose function can be understood in isolation. Rather, it is a dynamic and adaptive structure whose component polymers and regulatory proteins are in constant flux."[23]

Moreover, the organism's relatively fixed structures are themselves the *result* of flow, not the ultimate cause of it. My favorite example of this comes from my Nature Institute colleague, Craig Holdrege:

> Before the heart [in the human fetus] has developed walls (septa) separating the four chambers from each other, the blood already flows in two distinct "currents" through the heart. The blood flowing through the right and left sides of the heart do not mix, but stream and loop by each other, just as two currents in a body of water. In the "still water zone" between the two currents, the septum dividing the two chambers forms. Thus the movement of the blood gives the parameters for the inner differentiation of the heart, just as the looping heart redirects the flow of blood.[24]

The body, you might say, is a *formed* stream. And structures, once stably formed, do not necessarily stay that way. Many of the cell's membranes are continually yielded up to dissolution and replacement, or they are pinched off to form separate little compartments (called vesicles) containing special contents to be delivered somewhere else in the cell before they are dissolved. And the cell as a whole—even an undividing cell such as a neuron—may experience a complete replacement of its contents a thousand times or more over the course of its life. Many of the body's structures are more like standing waves than once-and-for-all constructed objects.

When examined closely, all parts of the organism reveal a dynamism integrated with their context. Consider mitochondria, the energy-supplying organelles found in cells. The individual mitochondrion is "highly mobile, squirming worm-like back and forth across the cell space

to places where energy is needed for special work." But it often dissolves into fragments, which then fuse with other fragments. "In fact, by placing a cell into a slightly acid medium, all its mitochondria can be made to break up into small spherical beads which, upon return of the cell to normal medium, merge again into strings eventually resuming the appearance and internal structure of a normal mitochondrion."[25]

Against the backdrop of context-dependent phenomena such as this, it is hardly possible to contend that we consist, from the bottom up, of machine-like *devices*. The idea reflects a dogma crystallized from a rarefied mesh of abstractions rather than an engagement with actual organisms. You might just as well find "machines" in the currents of a river. When scientists write that "Clock genes are components of the circadian clock comparable to the cogwheels of a mechanical watch,"[26] it ought to be scandalous. Yet such machine language is universal, is heavily relied on by otherwise rigorous scientists in their attempts to explain the organism, has no evident, serviceable meaning, and working biologists rarely if ever make a serious attempt to justify or even define it.

Nor are the points at issue even particularly subtle. Here is the heart of the matter: The parts of a clock are *put* together in a certain way; the parts of an organism *grow* within an integral unity from the very start. They do not add themselves together to form a whole, but rather progressively *differentiate* themselves out of the prior wholeness of seed or germ. They are growing even as they begin functioning, and their functioning is a contribution toward their growing. The parts never were and never are completely separate, never are *assembled*. A specific bit of food taken in from outside never becomes some new, recognizable part, added to the rest; rather, it is metabolically transformed and assimilated by the ruling unity that is already there. The structures performing this work, such as they are, are themselves being formed out of the work. Does any of this sound remotely like a machine?

When, on the other hand, we do build machines, we impose our designs upon them from without, articulating the parts together so that by means of their *external* relations they can perform the functions or achieve the purposes we intended for them. Those same relations give us our explanation of the machine's physical performance. If the behavior of one of the parts depends on internal workings, and if we cannot yet analyze those workings in terms of subparts and *their* external relations, then we regard the part as a temporarily unexplained "black box."

One reason we cannot explain the organism through the relations between parts is that those parts tend not to remain the same parts from

moment to moment. For example, as most molecular biologists now acknowledge, there is no fixed, easily definable thing we can call a *gene*. Whatever we do designate a gene is so thoroughly bound up with cellular processes as a whole that its identity and function depend on whatever else is happening. The larger context determines what constitutes a significant part, and in what sense, at any particular moment. Where, then, is any sort of definable mechanism? And the DNA sequence is just about the most rigidly fixed element the organism has to offer at the macromolecular level.

Certainly there are reasonable analogies between, say, our bones and joints on the one hand and mechanisms such as levers and ball joints on the other. Such analogies can be multiplied many times over throughout the human body. But to avoid falsehood it is necessary to add that these are only approximations.

Bones and joints are not in fact mechanisms. Bones, for example, are continually undergoing an exchange of substances with their environment, and even after the main period of our development is past, they are still being shaped and reshaped by their use or disuse and by the boundless range of other bodily processes with which they are interwoven. Astronauts on long missions in space lose significant bone mass, density, and strength;[27] lions raised in zoos have a bone structure differing from that of lions raised in the wild.[28] It's certainly true that mechanisms such as ball joints, levers, and cogwheels also suffer change—for example, through wear and tear. But, unlike bones, such mechanisms are not continually reshaped through the integration of their internal processes with those acting from without. Gears and levers are not *maintaining* themselves and *being maintained* in anything like the way an internal organ is.

The pervasive use of the machine metaphor, whether carelessly or by design, imports into biology ideas that have no place there. We have every right to ask the biologist who ceaselessly appeals to mechanisms, machines, and mechanistic explanations, "Please tell us what you *mean* by these terms." This doesn't seem unfair.

Trying to Grasp the Whole Organism

The special nature of biological understanding has been debated for as long as there has been a science of biology, with the debate taking form above all in the long-running dispute, on ever-shifting ground, between mechanists and vitalists. "Mechanism" has meant everything from "the physical organism is a machine, pure and simple" to "the organism is strictly material and is governed by nothing other than physical and

chemical processes." By contrast, vitalists have struggled to glimpse the "special something" that distinguishes living creatures from the non-living, whether it be some physical or quasi-physical "vital force" or simply principles of explanation that cannot be captured in the language of physics and chemistry even if those principles do not violate physical law.

That these are real issues, rooted both in the apparent distinctiveness of organisms compared to inanimate objects and in our direct awareness of our own life, and that the issues require some kind of resolution that has long escaped the discipline of biology, has been recognized throughout much of the past two centuries. Most biologists in recent decades have vested their hope in what seemed a near-certainty to them: their understanding of the organism would someday be reduced without remainder to the conventional terms of physics and chemistry. The case for that certainty having now become much shakier, any resolution of the long-standing debate seems as remote as ever.

The aspects of the organism triggering the whole dispute have commonly been associated with one or more of the following themes:

- *The peculiar unity of whole and part:* The form, existence, and activities of the parts depend upon, and arise from—are in some sense caused by—the whole, which is therefore expressed in one way or another through every part. This is much like the relation between individual words and their context—which is not surprising, since language is itself an expression of organic life.

- *Means-end ("purposive" or "final") relations:* Biological activities are carried out as if "with a view toward" or "for the sake of" some end. The organism "aims" to develop and sustain itself as a being with its own particular character. (I use quotation marks here because it is agreed on all sides that the directed aspect of biological performance should be distinguished from conscious human purpose, even if such purpose is viewed as a coming to intentional self-awareness of whatever expresses itself unreflectively in the wisdom of the body.)

- *The mutual (reciprocal) play of cause and effect:* Effects are not merely effects, but can simultaneously react back upon their causes. Or, as Kant puts it, the parts "should so combine in the unity of a whole that they are reciprocally cause and effect of each other's form."[29] To give an archetypal example, as the embryo polarizes into anterior and posterior, each pole is not only "opposite" to the other, but necessarily implied in the other. Each pole is properly formed only by virtue of the other's being formed. Neither is a unilateral cause of the other.

All three of these features are at least suggested by the rather simpler statement that we find in every organism a *meaningful coordination* of its activities, whereby it becomes a functioning and self-sustaining unity engaged in a flexible response to the infinitely varying stimuli of its environment. By virtue of this coordination, every local or partial activity expresses its share in the distinctive character of the whole. The ability of the organism to pursue its own ends amid an ever-shifting context means that causal relations become fluid and diffuse, losing all fixity. They are continually subordinated to, or lifted into service of, the *agency* of the organism as a whole.

There are no doubt many challenges to our understanding in all this, many issues to be clarified, perhaps even a new language to be worked out. But the starting point for this effort is clear: governance of the context over its separate elements, so frequently noted in the literature today, can be observed at every level, whether we speak of the organism, the cell, or the chromosome. The kind of wholeness we need to reflect upon was well illustrated by the pathologist A. E. Boycott in his presidential address to the Royal Society of Medicine's pathology section some eighty years ago:

> We generally think of the blood as something which goes round the body and in so doing brings food to the tissues, takes away their excreta and helps to keep them in communication with one another. But we may also think of it, and sometimes more profitably, as a tissue or organ whose chief business it is to be itself and maintain its own individuality. The blood certainly has a specific structure and a chemical composition, organic and inorganic, which is peculiar to itself. And it shows exquisitely that restorative response to injury which is the chief subject-matter of pathology. Within comparatively narrow limits of natural variations, the volume of blood, the concentration of red cells, the reaction, and so on are maintained at steady levels. Though almost every substance which goes into or comes out of the body passes at one time or another through the blood, its composition remains almost constant, and it is this individual characteristic which entitles us to have "normal" standards of hemoglobin, red cells, and the rest. All experience shows, too, that it is very difficult experimentally to produce deviations from these normal values of more than a fleeting character, and under a great variety of circumstances the blood persists in remaining itself.[30]

"Persists in remaining itself." The phrase may not quite rest comfortably with modern scientific sensibilities. Nor is it the only such phrase. But reasonable interpretations have long been on offer, as we will now see.

More Than the Sum of Its Parts

Variation of the parts amid relative constancy of a well-ordered whole that strives to remain itself: this was a central theme of one of the most prominent and now most unjustly neglected scientists of the past century. By all accounts a distinguished cell biologist, Paul Weiss pursued active research from the 1920s on into the 1970s, when he was awarded the National Medal of Science. He pioneered many techniques of tissue culture while pursuing important work in neurobiology, morphogenesis, limb and nerve regeneration, and cell differentiation. His awards and recognitions were many.

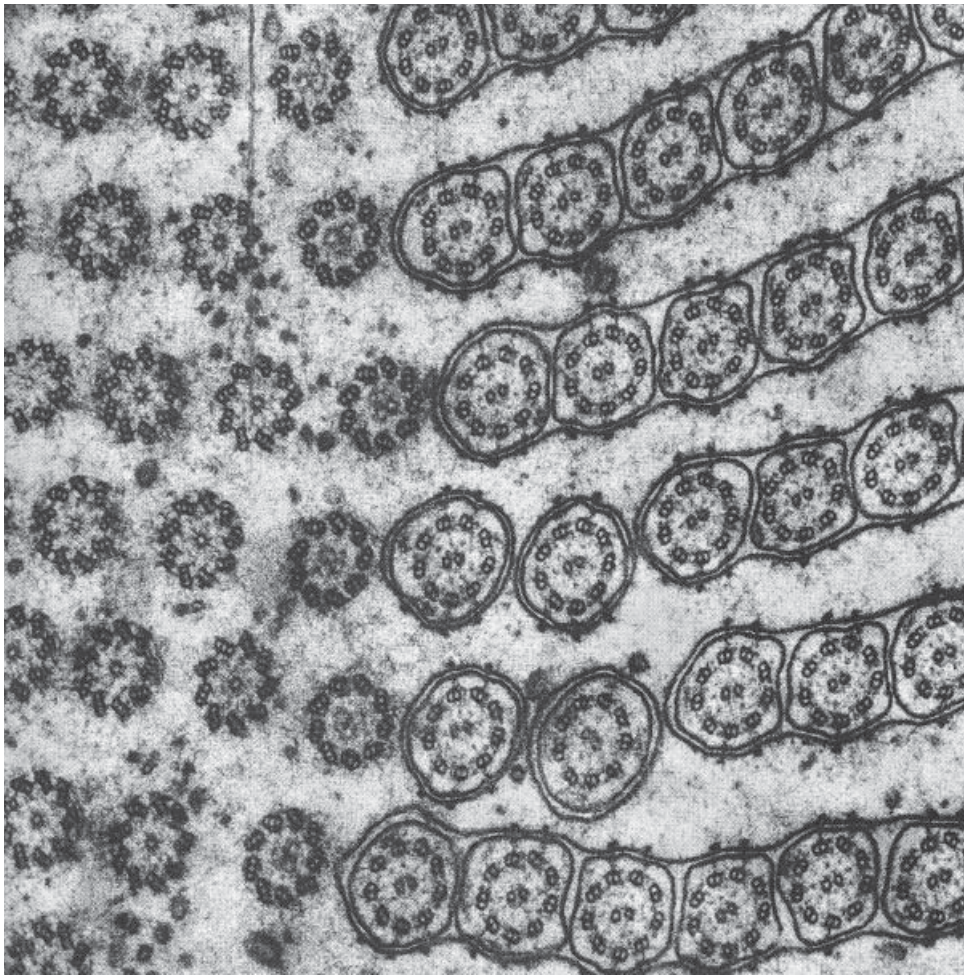
Before coming to America, Weiss received an "old-school" education in Austria, which may account for the fact that he was aware of certain broader issues in biology from the very outset of his career. A scientist's scientist in terms of his mathematical, experimental, and observational rigor, he couldn't help noticing organismal behavior that didn't fit the prevailing mechanistic models. For example, his powerful arguments against the gene-centered understanding of the organism, which we will touch on below, were founded on the most basic facts of observation and the most straightforward, unassailable reasoning—and they were arguments that would today be widely accepted. But at the time his was a voice in the wilderness; the almost arrogant confidence of molecular biologists, founded on deep philosophical commitment to the explanatory hegemony of the gene, prevented them from taking in his arguments. But now, if I'm not mistaken, there is a reawakening interest in what this rather low-key and incisive prophet had to say.

Picking up the theme of Boycott about the constancy of the blood amid change, Weiss provided numerous examples of global unity and harmony superimposed upon lower-level variation.[31] Consider the electron micrograph opposite, which shows a tangential section grazing the surface of a single-celled ciliate protozoan. Because the angle of the section is slightly oblique, the circular structures—each one a single cilium with eleven parallel fibers (nine in a circle and two in the middle)—are shown cut at varying depth, revealing different aspects of the structures. The placement and form of all the details shows no constancy. And yet that unevenness, which might be expected to lead to ever less order in the overall composition, is nevertheless disciplined toward a larger, patterned harmony.

Weiss shows repeatedly in his various analyses that the mechanical forces or physical dimensions or one-to-one interactions at the level of the parts of an organism are inadequate to determine the coherence of the scheme

into which the parts are fitted. We cannot compare the arrangement of cilia shown above to the way rigid, precisely shaped bricks can be laid out in a pattern determined by their shapes. Instead, as Weiss puts it, we see "certain definite rules of order" that "apply to the dynamics of the *whole* system… reflected in the orderliness of the overall architectural design, which cannot be explained in terms of any underlying orderliness of the constituents."[32]

Much the same applies to the pluripotent cells of the very young embryo. A given cell can be moved from one place to another, resulting in a completely different fate for that cell within the developing organism. What might have been part of a hand becomes instead part of a leg. This indicates that the cell's fate is determined "on the fly": a governing



An electron micrograph showing a cross section through the ciliary field of a protozoan, appearing in Paul Weiss, "From Cell to Molecule," *The Molecular Control of Cellular Activity*, 1962.

dynamic disposes of each part according to the needs of the overall pattern. The developing relations between the individual cells are more a result of than a cause of the order of the whole.

Besides its full complement of "genetic information," each cell needs still additional "topical information" derived from the structure of the collective mass, Weiss notes. How otherwise could any unit know just what scrap of information to put to work at its particular station in order to conform to the total harmonious program design? Left solely to their own devices, individual cells and their entrapped genomes would be as incapable of producing a harmonious pattern of development as a piano with a full keyboard would be of rendering a tune without a player.[33]

It is crucial to realize what Weiss is *not* saying. He is not saying that the laws of physics are violated in the formation of organic patterns. He himself spent many years elucidating the play of physical forces in such situations. What is being coordinated is nothing other than this play of forces. His point is that, whatever the level we analyze, from macromolecular complexes, to organelles, to cells, to tissues, to individual organs, to the organism as a whole, we find the same principle: we cannot reconstruct the pattern at any level of activity by *starting from the parts and interactions at that level.* There are always organizing principles that must be seen working from a larger whole into the parts.

Despite the countless processes going on in the cell, and despite the fact that each process might be expected to "go its own way" according to the myriad factors impinging on it from all directions, the actual result is quite different. Rather than becoming progressively disordered in their mutual relations (as indeed happens after death, when the whole dissolves into separate fragments), the processes hold together in a larger unity. The behavior of the whole "is infinitely less variant from moment to moment than are the momentary activities of its parts":

> Small molecules go in and out, macromolecules break down and are replaced, particles lose and gain macromolecular constituents, divide and merge, and all parts move at one time or another, unpredictably, so that it is safe to state that at no time in the history of a given cell, much less in comparable stages of different cells, will precisely the same constellation of parts ever recur.... Although the individual members of the molecular and particulate population have a large number of degrees of freedom of behavior in random directions, the population as a whole is a system which restrains those degrees of freedom in such a manner that their joint behavior converges upon a nonrandom resultant, keeping the state of the population as a whole relatively invariant.[34]

We might say that a given type of cell (or tissue, or organ, or organism) insists upon maintaining its own recognizable identity with "unreasonable" tenacity.

It turns out, then, that *less* change is what shows the whole cell or organism to be *more* than the sum of its parts. It is as if there were an active, coordinating agency subsuming all the part-processes and disciplining them so that they remain informed by the greater unity. The coordination, the ordering, the continual overcoming of otherwise disordering impacts from the environment so as to retain for the whole a particular character or organized way of being, expressively unique and different from other creatures—this is the "more" of the organism that cannot be had from the mere summing of discrete parts. The center holds, and this ordering center—this whole that is more than the sum of its parts—cannot itself be just one or some of those parts it is holding together. When the organism dies, the parts are all still there, but the whole is not.

Animistic Impulses in Biology

Consider also DNA and the vast array of proteins and other molecules that must cooperate with it in all its functions. A DNA molecule by itself is without meaning for the organism; it cannot *do* anything. As Harvard biologist Richard Lewontin once wrote, it is "a dead molecule, among the most nonreactive, chemically inert molecules in the living world."[35] Its meaning is as much a function of the molecules with which it interacts as it is a property of its own structure. Or, in Weiss's words: "Life is a dynamic process. Logically, the elements of a process can be only elementary *processes*, and not elementary *particles* or any other static units."[36]

But, we may ask, aren't all the molecules involved in these processes made by DNA?

Actually, no. First, as just noted, DNA by itself cannot make anything. Second, many crucial molecules that shape the functioning of the cell, including all lipids and carbohydrates, do not derive from DNA. This reminds us that the central functioning of metabolism—the transformation of nutrients in the cell—is not in any realistic sense *controlled* by DNA. The reverse is just as true; metabolic processes send signals to DNA when its services are wanted. Third, the proteins and noncoding RNAs that do derive from DNA are extensively and significantly modified by processes in the cytoplasm, with their functions depending heavily on these modifications. Fourth, the enzymes and other proteins essential for transcribing DNA certainly cannot be described as mere "products" of DNA because

they are never produced without already existing to help carry out the production. And fifth, DNA, far from being responsible for everything in the cell, is itself in an important sense the responsibility of the cell, which goes through a balletic drama of scarcely conceivable complexity in order to replicate and preserve this vitally important molecule.

In sum: all cellular constituents, including DNA, originate from the cell and organism as a whole.

To say, as Nobel laureate Max Delbrück once did, that DNA could be conceived in the manner of Aristotle's First Cause and Unmoved Mover, since it "acts, creates form and development, and is not changed in the process"[37]—well, that's a stupefying blind spot, a blind spot that to one degree or another dominated the entire era of molecular biology through the turn of the current century. It was already recognized and warned against by the German botanist Fritz Noll in 1903, who pointed out how (in E. S. Russell's paraphrase) "the chief theorists have tried to solve the problem of development by assuming a material and particulate basis [today's 'gene'], without however attempting to explain how the mere presence of material elements could exert a controlling influence on development. They have been forced to ascribe to such abstract material units properties and powers with which they would hesitate to credit the cell as a whole."[38]

Weiss emphasizes very much the same point: because there is no possible way to make global sense of genes and their myriad companion molecules by remaining at their level, researchers have "simply bestowed upon the gene the faculty of spontaneity, the power of 'dictating,' 'informing,' 'regulating,' 'controlling,' etc."[39] And today, one could add, there is at least an equal emphasis on how other molecules "regulate" and "control" the genes! Clearly something isn't working in this picture of mechanistic control. And the proof lies in the covert, inconsistent, and perhaps unconscious invocation of higher coordinating powers through the use of these loaded words—words that owe their meaning ultimately to the mind, with its power to understand information, to contextualize it, to regulate on the basis of it, and to act in service of an overall goal.

Weiss considers terms such as "regulate," "organize," and "control" an "obvious reversion in modern guise to animistic biology, which let animated particles under whatever name impart the property of organization to inanimate matter."[40] Weiss refuses to ascribe the power of regulating and organizing to specific material parts of the organism, which would grant them a kind of magical quality. Whatever regulates a set of interacting parts cannot be found in one of the parts being regulated. To see the principles of regulation governing any set of parts, we have to step back,

or up, until we can recognize a unity and harmony that operates, so to speak, *between* the parts, becoming visible only from a more comprehensive, relational vantage point.

This unity and harmony may represent a genuine difficulty for our understanding, if only because few in recent decades have bothered to address it. But until we see the problem where it actually lies, instead of concealing it in molecules with mystical qualities, we can hardly begin the work of trying to understand. To be sure, serious researchers long recognized the "problem" of biological explanation—but the issues were largely set aside in the era of molecular biology due to the expectation that they were well on their way to routine solution. Biology would soon be rid of its troublesome language of life in favor of well-behaved molecular mechanisms. And yet today, after several decades of stunning progress in molecular research, it is no more possible than it was two hundred years ago to construct a single paragraph of properly biological description that does not draw on a meaningful language of living agency considered improper in chemistry or physics.

If we want to reckon with the holism, the coordination and organization, the means-end relationships that are continually appealed to in biological explanation, one way forward might be to take the biologist's special language of life—minus its mystical tendencies—seriously and at face value. Perhaps the biologist describes what he actually sees, and perhaps the living qualities of the organism are not really as spooky as they are sometimes made out to be. Perhaps it never did make sense to try to understand the world from the bottom up, never made sense to dismiss the richest, most multifaceted phenomenal displays—the most organically unified realizations of the world's creative potential, such as we find in the performance of whole living creatures—as if they were, by very reason of the fullness of their revelation, the most unreal and misleading guides to the true nature of things.

Mechanisms of Control or a Living Unity?

Before concluding, it remains only to show ever so briefly what happens when you mix the language of organic coordination with that of mechanistic control. It's not a pretty sight. A paper that recently landed in my e-mail inbox, otherwise very worthy, serves as well as any to illustrate the situation. It concerns the p53 protein:

> The tumor suppressor p53 is a master sensor of stress that controls many biological functions, including [embryo] implantation, cell-fate

> decisions, metabolism, and aging.... Like a complex barcode, the ability of p53 to function as a central hub that integrates defined stress signals into decisive cellular responses, in a time- and cell-type dependent manner, is facilitated by the extraordinary complexity of its regulation. Key components of this barcode are the autoregulation loops, which positively or negatively regulate p53's activities.

We have, then, a *master sensor* that *controls* various fundamental cellular processes, and yet is dependent on the signals it receives and is subject to "extraordinarily complex" *regulation* by certain autoregulation loops. While all these loops regulate p53 (some positively and some negatively), one of them, designated "p53/mdm2,"

> is the master autoregulation loop, and it dictates the fate of an organism by controlling the expression level and activity of p53. It is therefore not surprising that this autoregulation loop is itself subject to different types of regulation, which can be divided into two subgroups.[41]

So the *master controlling* sensor is itself subject to a *master controlling* process (one of several regulatory loops) that *dictates* the fate of the organism. But this master loop, it happens, is in turn *regulated* in various manners (the author goes on to say) by a whole series of "multi-layered" processes, including some that are themselves "subject to direct regulation by mdm2"—that is, they are regulated by an element of the regulatory loop they are supposed to be regulating.

I can hardly begin to describe the stunning complexity surrounding and supporting the diverse performances of the p53 protein. But it is now clear that such "regulatory" processes extend outward without limit, connecting in one way or another with virtually every aspect of the cell. The article on p53 makes an admirable effort to acknowledge and summarize the almost endless intricacy and contextuality of p53 functioning and, with its language of mechanism and control, it does not differ from thousands of other papers. But that only underscores the undisciplined terminological confusion continuing to corrupt molecular biological description today. When regulators are in turn regulated, what do we mean by "regulate"—and where within the web of regulation can we single out a *master* controller capable of *dictating* cellular fates? And if we can't, what are reputable scientists doing when they claim to have identified such a controller, or, rather, various such controllers?

If they really mean something like "influencers," then that's fine. But influence is not about mechanism and control; the *things* at issue just don't

have controlling powers. What we see, rather, is a continual mutual adaptation, interaction, and coordination that occurs *from above*. That is, we see not some mechanism *dictating* the fate or *controlling* an activity of the organism, but simply an organism-wide coherence—a living, metamorphosing form of activity—within which the more or less distinct partial activities find their proper place. The misrepresentation of this organic coherence in favor of supposed controlling mechanisms is not an innocent inattention to language; it is a fundamental misrepresentation of reality at the central point where we are challenged to understand the character of living things.

How the organism holds together and makes sense is surely what the employers of such language are really trying to capture. One sympathizes with them. The problem is that their science gives them a respectable (and extremely valuable) language of *analysis*, while it is still stumbling around looking for a language able to comprehend *unities* or *wholes*—a "systems" language, some would say. The difficulty is owing to the stubborn proviso that this language must not come too uncomfortably close to infringing the taboo against recognizing mind and meaning, direction and intention, lest the world become unsafe for objects and mechanisms. So the researcher is left with a curious problem: to make *sense* of the organism without finding any real *meaning* in it—least of all the meaning traditionally associated with living beings. *Systems* may perhaps be tolerated; at least they are reassuringly vague and anonymous, and invite casual manipulation. But who knows what disagreeable entanglements might follow once we find ourselves staring into the face of other *beings*?

Notes

1. Sayyed K. Zaidi, Daniel W. Young, Amjad Javed, *et al.*, "Nuclear Microenvironments in Biological Control and Cancer," *Nature Reviews Cancer* 7, no. 6 (June 2007): 454-63.

2. Daniel R. Hyduke and Bernhard Ø. Palsson, "Towards Genome-Scale Signalling-Network Reconstructions," *Nature Reviews Genetics* 11, no. 4 (April 2010): 297-307.

3. Barbara McClintock, "The Significance of Responses of the Genome to Challenge," Nobel lecture, Dec. 8, 1983.

4. Christophe Lavelle, "Forces and Torques in the Nucleus: Chromatin under Mechanical Constraints," *Biochemistry and Cell Biology* 87 (2009): 307-22.

5. Jacques E. Dumont, Frédéric Pécasse, and Carine Maenhaut, "Crosstalk and Specificity in Signalling: Are We Crosstalking Ourselves into General Confusion?," *Cellular Signalling* 13 (2001): 457-63.

6. Emmanuel D. Levy, Christian R. Landry, and Stephen W. Michnick, "Signaling Through Cooperation," *Science* 328 (May 21, 2010): 983-4.

7. Bruce J. Mayer, Michael L. Blinov, and Leslie M. Loew, "Molecular Machines or Pleiomorphic Ensembles: Signaling Complexes Revisited," *Journal of Biology* 8, no. 9 (2009): 81.1-8.

8. Marcelo Behar and Alexander Hoffmann, "Understanding the Temporal Codes of Intracellular Signals," *Current Opinion in Genetics and Development* 20 (2010): 684-93.

9. Emmanouil T. Dermitzakis and Andrew G. Clark, "Life After GWA Studies," *Science* 326, no. 5950 (Oct. 9, 2009): 239-40.

10. Richard Dawkins, *The Blind Watchmaker: Why the Evidence of Evolution Reveals a Universe without Design* (New York: W. W. Norton, 1996), 120.

11. Stephen Rothman, *Lessons from the Living Cell: The Limits of Reductionism* (New York: McGraw Hill, 2002): 265.

12. Barry J. Grant, Alemayehu A. Gorfe, and J. Andrew McCammon, "Large Conformational Changes in Proteins: Signaling and Other Functions," *Current Opinion in Structural Biology* 20 (2010): 142-7.

13. Yaoqi Zhou, Dennis Vitkup, and Martin Karplus, "Native Proteins Are Surface-molten Solids: Application of the Lindemann Criterion for the Solid *versus* Liquid State," *Journal of Molecular Biology* 285, no. 4 (Jan. 29, 1999): 1371-5.

14. Vladimir N. Uversky, "The Mysterious Unfoldome: Structureless, Underappreciated, Yet Vital Part of Any Given Proteome," *Journal of Biomedicine and Biotechnology* 2010, article ID 568068. doi:10.1155/2010/568068

15. Jörg Gsponer and M. Madan Babu, "The Rules of Disorder or Why Disorder Rules," *Progress in Biophysics and Molecular Biology* 99 (2009): 94-103. doi:10.1016/j.pbiomolbio.2009.03.001

16. A. Keith Dunker, Christopher J. Oldfield, Jingwei Meng, *et al*., (2008). "The Unfoldomics Decade: An Update on Intrinsically Disordered Proteins," *BMC Genomics* 9, suppl. 2 (2008): S1. doi:10.1186/1471-2164-9-S2-S1

17. John S. Mattick, "Has Evolution Learnt How to Learn?" *EMBO Reports* 10, no. 7 (2009): 665. doi:10.1038/embor.2009.135

John S. Mattick, Ryan J. Taft, and Geoffrey J. Faulkner "A Global View of Genomic Information—Moving Beyond the Gene and the Master Regulator," *Trends in Genetics* 26, no. 1 (2009): 21-8.

18. John S. Mattick, "A New Paradigm for Developmental Biology," *Journal of Experimental Biology* 210 (2007): 1526-47.

19. Robert J. White and Andrew D. Sharrocks, "Coordinated Control of the Gene Expression Machinery," *Trends in Genetics* 26, no. 5 (2010): 214-20.

20. Gary C. Hon, R. David Hawkins, and Bing Ren, "Predictive Chromatin Signatures in the Mammalian Genome," *Human Molecular Genetics* 18, no. 2 (2009): R195-R201.

21. Kyle D. Mansfield and Jack D. Keene, "The Ribonome: A Dominant Force in Co-ordinating Gene Expression," *Biology of the Cell* 101, no. 3 (2009): 169-81.

22. Lenny Moss, *What Genes Can't Do* (Cambridge, MA: MIT Press, 2003), 95.

23. Daniel A. Fletcher and R. Dyche Mullins, "Cell Mechanics and the Cytoskeleton," *Nature* 463 (Jan. 28, 2010): 485-92.

24. Craig Holdrege, ed., *The Dynamic Heart and Circulation*, trans. Katherine Creeger (Fair Oaks CA: AWSNA, 2002), 12.

25. Paul Weiss, "The Living System: Determinism Stratified," in *Beyond Reductionism: New Perspectives in the Life Sciences*, ed. Arthur Koestler and John R. Smythies (New York: Macmillan, 1970), 361-400.

26. Urs Albrecht and Jürgen A. Ripperger, "Clock Genes," in *Encyclopedia of Neuroscience* part 3 (2009): 759-62.

27. J. H. Keyak, "Reduction in Proximal Femoral Strength Due to Long-Duration Spaceflight," *Bone* 44, no. 3 (2009): 449-453.

28. Craig Holdrege, "Seeing the Animal Whole: The Example of the Horse and Lion," in *Goethe's Way of Science*, ed. David Seamon and Arthur Zajonc (Albany: SUNY Press, 1998), 213-32.

29. Immanuel Kant, *The Critique of Judgment*, trans. J. H. Bernard (Amherst NY: Prometheus Books, 2000), II.1.65.

30. A. E. Boycott, "The Blood as a Tissue: Hypertrophy and Atrophy of the Red Corpuscles," *Proceedings of the Royal Society of Medicine* 23, no. 1 (Nov. 1929): 15-25.

31. Paul Weiss, "Cellular Dynamics," *Reviews of Modern Physics* 31, no. 1 (Jan. 1959): 11-20.

Paul Weiss, "From Cell to Molecule," in *The Molecular Control of Cellular Activity*, ed. John M. Allen (New York: McGraw-Hill, 1962), 1-72.

Paul Weiss, "One Plus One Does Not Equal Two" and "The Living System: Determinism Stratified," in *Within the Gates of Science and Beyond: Science in Its Cultural Commitments* (New York: Hafner, 1971), 213-311.

32. Weiss, "The Living System: Determinism Stratified."

33. Paul A. Weiss, *The Science of Life: The Living System—A System for Living* (Mount Kisco NY: Futura Publishing, 1973).

34. Weiss, "From Cell to Molecule."

35. Richard C. Lewontin, "The Dream of the Human Genome," *New York Review of Books* 39, no. 10 (May 28, 1992), 31-40.

36. Weiss, "From Cell to Molecule."

37. Max Delbrück "Aristotle-totle-totle," in *Of Microbes and Life*, ed. Jacques Monod and Ernest Borek (New York: Columbia University Press, 1971), 50-5.

38. Edward Stuart Russell, *The Interpretation of Development and Heredity: A Study in Biological Method* (Oxford: Clarendon Press, 1930), 287.

39. Weiss, "The Living System: Determinism Stratified."

40. Weiss, "From Cell to Molecule."

41. Xin Lu, "Tied Up in Loops: Positive and Negative Autoregulation of p53," *Cold Spring Harbor Perspectives in Biology* 2, no. 5 (May 2010): a000984.