Organisms and Their Evolution

Agency and Meaning in the Drama of Life

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The book will remain for the foreseeable future a “living document”, which is an impressive way of saying merely that it will be subject to change. Some of those changes may result from your comments, if you are so kind as to send them to Stephen L. Talbott (stevet@netfuture.org).

Table of Contents

Part 1: The Life of Organisms

TECHNICAL SUPPLEMENT TO PART 1

Part 2: Extending the Organism’s Story:
Toward an Evolutionary Narrative

Part 3: The Underpinnings

Preface

I see a crow, perched atop a shagbark hickory tree about fifty meters in front of me. It seems oddly unperturbed on its branchlet as it surfs the tumultuous waves of a stiff wind. The winds, of course, are its own element, just as the twisting currents of a swift stream belong to the trout. The crow, I reflect, is its own sort of master of the wide domain it surveys — a domain whose whole aspect is unfamiliar to me. As I walk, I try to see myself through its unhuman eyes, a small, insignificant figure approaching far below, passing beneath, and then slowly receding into the distance.

I was once taught to see myself this way when in the presence of a bird on high — I, an intruder moving for a few moments through another's native landscape. It was a modest little exercise in becoming detached from one's own point of view. I suppose it's rather easy for us today. We are, after all, heirs of Copernicus, whose one giant leap for mankind sprang from his then-novel capacity to project himself, as an observer, onto the surface of the sun. From that viewpoint he could imagine his own, troubled earth moving serenely through space.

But Copernicus had only to project himself through what was in the process of becoming, for us, "empty space". How much more difficult to insert oneself into the "mind" of a crow! Who is it that looks down at me, and from what strange, inner world does it gaze? What would I *really* be seeing if I could see with crow-vision, so penetrating in its crow-ness, yet so alien to me? I have to admit that there is vastly more of myself projected to the top of that tree than there is of the crow. When the lives of distantly related beings are at issue, isn't getting outside one's own viewpoint all but impossible?

My primary aim in this book is to enable the reader to see organisms — and especially animals, which are my main examples — with new eyes. In place of a systematic survey, I present what might almost be approached as a series of re-visioning exercises whose diverse focal points, so I hope, can merge for the reader into a single, coherent landscape. It will be a landscape viewed, so I also hope, from unexpected angles.

The oddity lies in the fact that I rely rather heavily on topics drawn from molecular biology, a discipline that gives us no real landscape at all — certainly not one based on the kind of direct, sensible experience the founders of the Scientific Revolution craved. The biologist's picture of atoms and particles is synthesized from theoretical constructs and outdated mental pictures that, especially in the physics of the last hundred years, have been thoroughly subverted. So how we should actually *picture* what I will refer to as the "microworld" is a genuine mystery today.

The problem is that biologists have been content to stick with nineteenth-century images of the solid little "particles" that were debunked in physics long ago. And so they imagine a cell full of little materialized "molecular machines", however tiny. Where physicists have acknowledged many wide-open questions at the foundation of their discipline, biologists have doubled down on a rather crude materialism.

But the biologists' problem is a problem for this book as well. How can I focus as much as I do on a field of research (molecular biology) that is more or less a blank slate so far as an experience-based (empirical) science is concerned? Am I not just lending further support to a kind of biological fantasy world?

I am inclined to plead guilty to this charge. Of course, I do at times try to warn the reader against misconceptions — for example, in Chapter 15 ("Puzzles of the Microworld") and Chapter 21 ("Inheritance, Genetics, and the Particulate View of Life"). But there are also at least three strong, positive justifications for looking carefully at how biologists appeal to molecular-level research as a bottom-up foundation for understanding organisms. These all have to do with the fact that molecular biology presents to one's imagination a kind of blank slate. Looking at what researchers have projected onto this blank slate can tell us a great deal about the character and pathology of biological thought today:

To begin with, we see a seemingly unquenchable thirst for unambiguous (and therefore unbiological) cause-and-effect explanation. These explanations tend to be of an antiquated, billiard-ball sort involving particles that, as physicists have long known, simply aren't there — certainly not in the way they are being imagined within biology. In this way we come to those ubiquitous and hopelessly misconceived "molecular machines" that are supposed to perform the fundamental living work of organisms.

The fact that biology as a whole has been thought to be securely grounded in molecular-level explanation tells us a great deal about the distortions of this particular science. It tells us more, that is, about the minds projecting their preconceptions upon the unknown, mysterious molecular background than about organisms as such.

In the second place, because so much of molecular biology is based on non-empirical, unsupportable, and metaphysical (materialist) assumptions, the supposed explanations issuing from molecular biology never add up. When we look at these explanations, we easily recognize the confusion at work in them. (See, for example, Chapter 8 ("The Mystery of an Unexpected Coherence") and Chapter 9 ("A Mess of Causes").

Recognizing the confusion can, in the third place, point us in the direction of a more adequate understanding — one that starts with the observable organism rather than a fantastic, non-observable realm littered with metaphysical "projectiles". I gesture toward the grounding principles of such a fuller understanding in Chapter 13 ("All Science Must Be Rooted in Experience"), Chapter 24 ("How the World Lends Itself to Our Knowing"), and Chapter 25 ("Some Principles of Biological Understanding").

I have, throughout the writing of this book, been accompanied by a discomfiting awareness of the difficulty of the task I have set myself. This is presumably due mainly to my own limitations. Seeing things anew — as opposed to collecting more and more data and trying to assemble it into unambiguous demonstrations of truth — is not something I find easy, nor is it something we are generally encouraged to strive for today. The following thoughts, borrowed from others, have, for me, emphasized the great distance from routine claims of truth to genuine profundity:

- The first of these thoughts is an overall conclusion drawn from a study of meaning entitled *Poetic Diction*, written in 1928 by the philologist and student of the evolution of consciousness, Owen Barfield. It expresses a truth also forced upon me directly by many less-than-satisfying efforts at communication. (The phrasing is my own:)

> *If a conversation takes place primarily as a logical contest or as a battle of "proofs", rather than as an effort to clarify, shift, and deepen meanings, it is likely to be shallow.*

In my run-up to writing this book — and throughout the writing — I have had to suppress my own deeply rooted, almost congenital instincts toward doing intellectual battle. I now know that victory in this particular struggle with myself will never be fully won.

◆ Then there is my vague remembrance of a remark I somehow associated with the late physicist, Georg Maier. It ran more or less like this:

> *If you think you have reached a point where you can cleanly explain a profound truth, you do not yet understand it.*

After the first appearance of this preface, my colleague, Henrike Holdrege, gave me an actual quotation from Maier, which serves just as well: *"the knowing of a phenomenon (appearance) is not at all completed by a successful explanation".*

◆ Finally — again from Barfield, and this time as a direct quote wrapped up with a striking metaphor — there is this:

> *"If you take your view of the world seriously, to air it is tiring. Moreover, in any ordinary conversation you can only do so very superficially, and your own heard superficiality wounds you. The opinions, whether firm or tentative, of a man over fifty who has thought for himself about the nature of man and the universe will have acquired a certain depth and weight that make them ill adapted for point-blank encounter. Submarines rarely engage one another in battle"* (Barfield 1965, p. 74).

If you want to have a fruitful conversation with someone, the two of you must meet upon some sort of common ground. For if you see things in such fundamentally different ways that every assertion from one side is met by a refusal to accept it on the other side, then there is not much reason to talk. If, on the other hand, the two of you are so close in thought and assumption that you mean the same thing with your words and can work with precisely the same set of facts, then the role of conversation is also limited. All you need to do is to order the facts in such a way as to prove your case to the other person. Nothing really new will arise, because your proof was already implicit in your mutually accepted understanding of things.

But there is a potentially productive middle ground where enough is shared to make conversation possible, and enough is not shared to raise the hope of genuinely new insight. In this case the challenge is to hear the other person's words and facts with new ears. We can most easily open ourselves to this possibility if we have managed somehow to get outside our culture's "common sense", much as we today are able to challenge, or even laugh at, the received and unquestioned wisdom of previous historical eras. Managing to see our own culture in such a foreign light, however, can be an almost impossible task. But even a small effort in that direction can be life-changing — like being let out of a prison you hadn't realized you were in.

I do not expect my efforts here to be adequate. But I do hope they may be of some use to those sympathetic readers seeking a new vantage point upon biology — one that, even if at first it presents an unfamiliar and perplexing landscape, at least does not require us to deny the living experience of all creatures, including ourselves.

Sources

Barfield, Owen (1965). *Unancestral Voice.* Middletown CT: Wesleyan University Press.

Barfield, Owen (1973). *Poetic Diction: A Study in Meaning.* Middletown CT: Wesleyan University Press. Originally published in 1928.

Chapter 1

The Keys to This Book

We begin with a vignette drawn from a single activity of just one from among the millions of species with whom we share the earth. This description is taken from the biologist, novelist, and science philosopher, E. L. Grant Watson, who in turn is compactly summarizing observations by one of the world's great entomologists, who lived during the late nineteenth and early twentieth centuries:

Box 1.1

The Enigmatic Wisdom of the Potter Wasp

Figure 1.1. An unidentified species of *Eumenes*.[1]

"Among the fascinating stories of animal life told by the French naturalist Henri Fabre is that of the [potter wasp] *Eumenes*. The fertilized female builds a little domed house of sand spicules on some stone or rock foundation. The foundation ring is traced in minute pebbles. On this she builds a series of concentric rings, each diminishing in circumference, so as to enclose a domed space. At the top she leaves a hole. She then begins collecting certain species of small caterpillars. She stings these into a partial paralysis, but does not kill them, for they will be needed as fresh meat for the young she will never see.

"When the wasp has collected either five or ten caterpillars, she prepares to close the dome, reducing the size of the hole. She now goes through a complicated process which would seem to indicate foresight on her part. Yet she has no foresight, only a highly developed instinct. From her ovipositor she excretes a juicy substance, working it with her legs into a narrow, inverted cone. With a thread of the same substance, she stitches the cone to the top of her domed building. Into the inverted cone, she lays an egg. She then seals up the hole, leaving the egg safe within the cone, suspended on a thread. This done, she goes off and builds another dome to repeat the same cycle of events.

"In a short time the egg hatches into a tiny, white grub, so helpless and delicate that if placed among the still-living caterpillars on the floor of the dome, it would inevitably be injured. In its cradle it is safe. When hungry it spins a thin thread of its own, on which it descends and takes a bite of caterpillar. If the wriggling caterpillars appear threatening, it can retreat up the thread, and wait. In this way the grub spends its infancy; but, as it grows stronger, it risks a final descent, and devours, at its leisure, the still living food that mother has so satisfactorily provided.

Figure 1.2. Nest of a potter wasp on top of a concrete wall.[2]

"From the domes that contain five caterpillars male wasps emerge; from where there are ten caterpillars, the larger female wasps. This raises an interesting question: Does the amount of food determine the sex? The mother wasp, who appears throughout her lifetime as a highly nervous and brilliantly alive creature, has built just the right sort of houses for the offspring she will never see; and has provided just the right amount of food. She is singularly well-adapted for her life; she stings the caterpillars just enough to keep them quiet, but not enough to kill them; she packs each dome with the right amount of food for male or female grub. The suspended cradle protects the tender infant from the rough reactions of the caterpillars while being eaten. Everything is in order, and as the emerging wasp dries her wings in the summer sunshine, she must surely feel that God is in his heaven, and all is well with the world. The caterpillars might harbour different sentiments …" (Watson 1964, pp. 85-86).

And so (focusing on the wasp's offspring) we picture in our imaginations a minuscule creature, with the nascent intelligence of an insect newly hatched from its egg, immediately setting out upon a journey by descending an almost invisible, yet reliably strong thread spun by itself — all *because* it needs a bite of food. And it then quickly retreats back up the thread (a remarkable physical feat; how does it done?) *because* its existence is threatened by larvae far more massive than itself.

That word "because" — *due to the cause of* — is central to a science concerned with the causes of things. But the usage here, referring to a creature's *need* and its *effort to preserve its own existence*, is as far removed from the word's preferred scientific employment as the little drama of the potter wasp's performance is from the events of the nonliving world. Purely physical stuff is not characterized by need, effort, or a drive toward self-preservation.

This difference between living and nonliving is not one that many scientific students of life are fond of. That is why they have invented an abstract evolutionary drama of miraculous character in order to explain the difference away. As Lila Gatlin, a prominent biochemist, mathematician, and shaper of evolutionary theory in the twentieth century, once acknowledged, "The words 'natural selection' play a role in the vocabulary of the evolutionary biologist similar to the word 'god' in ordinary language" (quoted in Oyama 2000, p. 31). In effect, the organism's living wisdom was transferred to an omnipotent "force" of evolution, where it could be kept safely out of sight, obscured behind an elaborate technical and mechanistic terminology.

An aim of this book is to recapture the drama of life in the place where it actually occurs — in organisms themselves — and to lay bare as clearly as possible the failure of the reigning evolutionary theory to explain the special qualities of that drama. This will be a matter of showing that, in a primary sense, the life of organisms explains evolution, rather than being explained by it.

Meanwhile, all may agree that our wonder at the potter wasp's behavior is perfectly natural. So also is a strong sense of recognition: we have learned to *expect* such astonishing achievements in the living kingdoms. We know that every sort of organism, if only we observed it closely enough, would reveal fascinating and almost inconceivable capacities to thrive in its unique life circumstances. Even staying with the potter wasp, we would rightly be confident of the further marvels we would encounter if we looked into its mating and reproductive processes, or inquired how it *perceives* a world and effectively navigates the features of that world. Or how it searches out prey for its young. Or how its body gains and sustains its staggeringly intricate and complex physical form, all the way down to the pattern of its molecular interactions.

We find ourselves woven into a fabric of earthly life so diverse and luxuriant and nearly incomprehensible in its wondrous displays that we cannot survey or even imagine a billionth part of it. But then, too, there is this: the wasp's capacities, like those of countless other creatures, seem in some regards wholly routine, familiar, and even human-like to us. In fact, they so powerfully remind us of our own skills and intelligence that we are continually tempted to project our own sort of experience onto other organisms.

On one hand, no scientist would — or should — say, with anything like the human meaning and feeling of the words, "The potter wasp takes great care to make thoughtful provision for its young". On the other hand, we can hardly avoid our scientific responsibility to ask, "How is it that the performance of the potter wasp so forcibly reminds us of what, in our own evolutionary development, has become 'taking great care to make thoughtful provision for our young'? Do the two kinds of behavior arise from wholly disparate roots in the history of life on earth, despite appearances?"

Perhaps the best place to start answering that question is with a resolve not to compromise any side of the truth merely because we are philosophically uncomfortable with its apparent implications. In particular, we ought not to twist our understanding out of shape due to a historically conditioned revulsion against anything like a purposive dimension to life processes. Nor should we be unwilling to acknowledge the ways in which all organisms behave as more or less centered agents in the world. Nor again ought we to respect any presumed rule in biology that says, "Some human traits are unnatural and cannot be referred to in a properly 'naturalized' science".

Oddly, those who most eagerly remind us that "humans belong to the animal kingdom" often seem the ones most reluctant to embrace the flip side of this truth: all animals have arisen within the same drama of evolving life that, we now know, also happened to be in the business of producing humans. If we want to say that humans share in the nature of all animals, how can we then turn around and ignore the obvious implication that all animals share something of the nature of humans?

Here I would like to summarize, ever so briefly, certain themes suggesting what sort of book you are reading:

THEME #1: NARRATIVE

Meaningful life stories are the primary subject matter of biology.

Every organism is weaving a life story — or, perhaps better, is actively *participating* in a life story, a meaningful narrative. The description of the potter wasp above is one episode in such a story. Such stories are future-oriented in the manner of a historical narrative. It's not for nothing that biologists find themselves speaking so often of an organism's *development* — a word they would not use in the same sense for geological strata or clouds. Biological narratives tend at all times to express meaningful activity in which the organism progressively realizes its own potentials.

We may often think of these narratives as thoroughly intentional, task-centered (end-directed), and carefully planned. This is highly problematic, since organisms do not, in the human sense, plan their actions. Nevertheless, there is something unavoidable in this usage. Organisms are not *wholly* other than humans. We do witness in every organism a striking coordination of diverse means in the service of its own needs and interests — a coordination that is generally contextualized within a larger community of beings and interests.

The capacity for story-like, "directive" activity in living beings (see the definitional hints below) is simply what we observe. It remains there for us to observe regardless of whether an organism conceives intentions for itself in a human-like fashion. The bare fact of *something like intention* is written all over the potter wasp's behavior. If our own scientific understanding teaches us to avoid the all too natural but wrongheaded idea of a "goal" being "aimed at", this should not scare us away from seeing the full sense of the wasp's performance in its own evident terms, or prevent us from acknowledging the playing out before our eyes of a remarkably apt and moment-by-moment, *presently active* wisdom.

In Chapter 25 we will look at the distinction between *owning* one's intentions in the rather free and conscious way we humans do (when we are fully awake), and (more like the wasp) being *owned by* them. These are very different conditions, and the difference is one we might want to think about. After all, we ourselves can sometimes become aware of meanings and intentions that once lay far below (or above?) our conscious willing and planning, and that therefore possessed us more than the other way around.

Much of what I have just said requires us to acknowledge the organism — and particularly every animal — as a focal *agent*, a being capable of weaving and inhabiting its own story, and a being whose causal activity is locally centered and distinct from the more general regularities we observe in the inanimate world. At the same time, every organism's story is interwoven with that world, taking on its substance and lawfulness as the very means for its own self-expression.

THEME #2: INTERIORITY

Every animal's life narrative is an outward expression of interior meaning.

It may be that when humans communicate, there is nothing (apart from certain instances of spoken and written language) more richly and specifically informative than the expressions of the human face. Much of our life is shaped and guided by the facial expressions all around us. All that these expressions tell us, however, cannot be encompassed by the physical-causal terms of facial musculature, skeleton, and flesh. That which bears the expression is indeed outward, material, and physically lawful. But what is expressed is, we can reasonably say, *interior*. Sadness, pensiveness, elation, doubt, anger, vexation, impatience, uncertainty, satisfaction — these possess, at least in part, a non-spatial character. Or again: while the material embodiment of what is expressed is both real and spatial, what is expressed *through* the outward manifestation is real but not spatial. So the word "interior" is problematic; it typically suggests a spatial relation, whereas I am using it to suggest something like "not *out there* in a spatially locatable sense".

We look through and by means of the face as a material manifestation in order to see the interior meaning that is being expressed. It is much the same as with spoken words, whose interior meanings are not revealed so long as we are noticing them only as sense-perceptible sounds. We must "hear through" the sounds so as to grasp their immaterial meaning.

But it is not just humans. All living performance expresses one or another form of interiority. In our own case: if I walk to the corner store in order to buy a gift for a grandchild, what I am doing can never be captured by what we think of as a purely physical description of the movement of my legs and arms, vocal apparatus, and so on. So, too, with an animal engaged in anything we would call "behavior". The meaning of the behavior — whether a courtship ritual, or burial of food, or tracking of a scent, or digging of a burrow — can never be described in strictly physical terms (if such strict terms are ever possible).

Further, as I try to suggest throughout this book, even our descriptions of cellular and molecular "behavior" refuse to be altogether cleansed of interiority. We can always recognize a *meaning* — what a biological activity is *about* (synthesis of a protein, or extraction of usable energy from a substance) — when we look at cellular goings-on, and our biological inquiries are guided by this meaning. Meaning itself is never spatial or sense-perceptible, even if spatial structures are required for giving material expression to meaning.

A dramatic fact about contemporary biology is that biologists seem to have a horror of interiority, or the non-spatial and non-sense-perceptible. Given that the *life* of animals is through and through an interior business, this horror is not only perplexing, but also devastating for the prospects of a truly biological science.

THEME #3: HOLISM

The meaningful, narrative character of life demands its own style of understanding and explanation.

If the organism's life, its biological existence, takes *narrative* form, then our explanation of its life — contrary to conventional notions of explanation — must also take a narrative form. And since a genuine, living narrative is always a playing out of *interior* meanings, the explanation must be framed in terms of those meanings.

It could hardly be clearer that the elements of a story, like the elements of an organism's life, can never be considered adequately in isolation from each other. Nothing is absolutely distinct from everything else. The end of a really great novel will be illuminated by its beginning, and the beginning by the end. This interwovenness of the narrative amounts to a kind of holism, and in this respect might far more appropriately be compared to sketching a portrait than to analyzing a machine into discrete parts and causal relations.

However, it is clear that we cannot have holism without also applying the remarkable analytical skills that we humans have so fruitfully gained. It is hard even to conceive how one might sketch an organic whole without having a lucid and detailed awareness of its parts. The need is to hold together the two movements of thought — the synthetic (holistic) and the analytical.

A supposed advantage of the one-sided striving for a strictly physical description of the world is that it depicts for us (or so we imagine) things that can be separated from each other, physically or notionally — and then counted. This gives us at least the pretense of a quantitative science, free of qualities and meaning. It also lays the basis for a method of reductive analysis. Things are analyzed into discrete parts, those parts are then analyzed into sub-parts, and so on.

Presumably the process stops at some significant bottom. But what if, having gotten there, we still have not characterized anything in its own terms? If our analytical descent hasn't led us to a fundamental reality of which we can say, "I now know what that sort of thing is", where would the significance of the entire process lie?

If there is to be a counter-movement to analysis, it depends on things *revealing something about themselves*, so that we can do more than merely refer them to still other, smaller things. So long as we merely say, "This thing consists of such-and-such other things", and the other things, rather than being characterized in their own terms, are said to be constituted by still other uncharacterized things, we do not have any *this* or *that* at all. If nothing "speaks" to us of its own character — if all we have are words that are our own, bare, meaningless labels for a mute whole and its mute parts — then we have no hope of scientific understanding.

And something like this appears to have happened. Instead of landing at the end of our analysis in bedrock, supportive, and knowable territory, we have actually found ourselves in an alien place, where we can say virtually nothing from experience and observation about what is "really there". Particle physicists have an interesting story to tell biologists about the perplexities encountered at the bottom — so "interesting", in fact, that the effort to describe the relevant phenomena in meaningful words is often considered disreputable in physics. As the physicist Robert March put it:

> We should never have expected words born in the familiar world readily accessible to our senses, such as *particle* and *wave*, to perfectly describe the microcosm. The electron is what it is, and if the words we use to describe it seem full of paradox, *so much the worse for those words*. The equations have it pinned down neatly (March 1977, p. 235).

Unfortunately, equations alone do not give us a material world, but only a realm of discarnate thought.

The interesting thing, however, is to notice how our science rises above such emptiness. We do say meaningful things in science, and this is because the meaningful counter-movement to analysis is inescapable — although generally not noticed for what it is. After all, in order to analyze a whole into parts, we must first have recognized each part as significant — as a meaningful whole in its own right. This recognition of wholes, however unconscious it tends to be, is fully qualitative, contrary to our usual ideas of science (Chapter 24), and it requires a movement of understanding that runs contrary to analysis.

The synthetic, or holistic, counter-movement to analysis is implicit in the biologist's frequent reference to the "context-dependence" of biological processes (Chapter 6). The problem is that the implication here — the implication that there is a kind of influence or causation running from a collective, complex whole toward its parts — has drawn little reflection and has had little effect on the underlying assumptions of biologists. "Context" is one of the most common words used by geneticists and molecular biologists. But it seems that no one is at all interested in asking what the term means and implies.

In this manner, "holism" — despite its being hardly separable conceptually from "context" — has become a kind of "devil word" in biology, a fact ironically coexisting with a refusal to consider the issues implicit in current, context-centered biological language.

In this book "holism" — like the the biologist's more acceptable and virtually equivalent "context-dependence" — will simply be taken for granted from the beginning. But, unlike "context-dependence", its meaning will be consciously and explicitly drawn out as we go along.

THEME #4: BLINDSIGHT

A kind of blindsight is evident in much of biology.

Living narratives, as observed, for example, in all animals, are in fact recognized within biology. For example, they provide the structure for research projects. These typically have to do with how an organism accomplishes this or that function, or *task*, such as obtaining food, or maintaining bodily temperature at an acceptable level, or, in the case of many cells, achieving cell division. (Rocks and streams do not have tasks.) But something rather like a taboo seems to require biologists to ignore all this in their scientific explanations. They are allowed to discuss only physical "mechanisms" that make *no inherent reference* to — and therefore do not explain — the task-nature of the problems that prompted biological inquiry in the first place.

In fact, most biologists speak in many contexts as if they were unaware of what they actually know about the organism's end-directed activity. This is understandable: it is easy to see how the cognitive dissonance between what they intuitively know of organic agency and what the taboo allows them to say (or think) in their biological explanations might prove intolerable if brought fully to mind.

This might bring to *our* minds the curious and well-known phenomenon called "blindsight". It works like this. Suppose there is a certain life-sized statue on the floor of a museum I am exploring. If I suffer from blindsight and am asked about the statue, I might truthfully reply, "What statue? I don't see anything there." But then, in wandering about the room, I am observed always to walk carefully *around* the statue rather than bump into it. Clearly, in some sense I do see it, even while remaining consciously unaware of (and even denying) what I see.

My suggestion, then, is that something analogous to this phenomenon works powerfully within biology today. Biologists carefully walk *around* the fact of the animal's narrative agency, even while every biological (as opposed to physical and chemical) question they ask affirms their *knowledge* of this agency. One result is that much about the true character of animals (and organisms generally) comes through in the biological sciences despite the biologist's explicit denials. Bringing attention to the great mass of obscured truth already "seen", if only blindsightedly, is a lot of what this book is about.

But another result of blindsight is that, so far as explicit theory and philosophy are concerned, biology suffers from the deepest possible distortions. We end up with living processes *theoretically* stripped of their life — this despite the fact that we ourselves know this life more directly and intimately than we know anything about the non-living world.

What is needed, according to the late Harvard geneticist, Richard Lewontin, is for biologists "to take seriously what we already know to be true" (Lewontin 2000, p. 113).

Some definitional hints about key biological terms

A number of the terms central to this book are foreign to conventional biological usage. The strangeness in this, I dare to say, is on the part of biology rather than this book. In general, I try to employ the following words in agreement with their use in common discourse as far as possible — and not to tie them down with overly artful precision. I hope that the meanings will become more specific — or more flexible — based on their various contexts of use.

Agency. Humans are agents — we possess agency, because we possess an awareness of our world and can act in it. We help to create the situations in which we live, instead of merely being determined by them (Welburn 2004, pp. 263-64n17). The cells of our bodies clearly can participate in our agency by giving expression to it, as when we move our limbs intentionally. But we would never say of those cells as such that they possess awareness or agency, as opposed to moving with an agency not fully their own. This is suggestive of the kinds of distinction we must make between ourselves and, say, single-celled organisms.

I know of no reason *not* to believe that, just as the intentions of a human individual play through trillions of cells, so also collective intentions can play through the bacteria in a bacterial film (evident, for example, in "quorum sensing"), as well as through the members of a termite colony, or any species at all so far as its members share a common way of being — and indeed in human society in ways of which we are scarcely conscious.

Archetype. The archetypal idea of an organism is its dynamic, adaptive, evolving way of becoming and remaining true to itself.

Atoms/Molecules. You will find comments here and there in this book suggesting something about the unreality of atoms and molecules. The effort is to emphasize that in the submicroscopic realm we are dealing with theoretical constructs that do not have the reality required by an empirical science — the reality of sense-perceptible experience. The problems arise, as physicists well know, when we endow such constructs with imagery derived from our experience of the material world. Then we are dealing with invented unrealities, and these tend to mock us when we try to make sense of our experiments.

I attempt to show in Chapter 24 that we have little choice but to assume that the only reality the world possesses is the reality appearing, and only appearing, in all the possible forms of *experience*. To make any other assumption is to speak ignorantly — to talk about what we do not *know from our own experience or anyone else's experience*. The nice thing is that when we do make the necessary assumption, it begins to justify itself in our understanding with gratifying fullness.

Blindsight. See Theme #4 above.

Directive. E. S. Russell, a marine biologist and philosopher of "organismal biology" during the first half of the twentieth century, adopted the word "directive", as in the title of his wonderful book, *The Directiveness of Organic Activities* (Russell 1945). He chose a less familiar word in order to encourage in his readers an awareness of the distinctions between human end-directed activity and the activity of animals. I will, in part, follow suit, although I will also freely use "directed" or "end-directed" in the conviction that we need to cultivate, not only an awareness of the *differences* between humans and animals, but also of the *connections*.

Biological activity *is* directed in the immediate sense of the word — directed in the way the development of a squid or fox or ape is directed from the zygote toward the adult form, and will take extraordinary steps to achieve that form in the event of a disturbance. This remains true even though the process is not at all consciously directed in the manner of our own willed activity. For that matter, neither is our human movement from zygote to adult form consciously directed. See also "*telos*-realizing" below.

Holism. See Theme #3 above.

Integral unity of the organism. I use something like this phrase often, and intend it as an active concept in Aristotle's sense of "being at work staying itself" (in Joe Sachs' translation of Aristotle's *entelecheia* — Sachs 1998, p. 245). Through this activity, the parts of an organism arise from and are differentiated from out of a whole, not assembled as pre-existing entities in order to build a whole. The integral unity is actively there from the start, and is not at any point imposed from outside. It is a unity because each part reflects — or participates in and remains consistent with — the nature of the whole from which it arose.

Intention/intentional. I try to use these words as far as possible in their routine, day-to-day meaning. We recognize intentions by observing the guiding principles and meanings at work in an activity. It needs noting, however, that we humans can "intentionally" do something not only through careful planning, but also unconsciously, as when we notice a traffic irregularity while driving a car and engaging in conversation, despite the fact that we were paying no conscious attention to the road. It is much the same when we ride a bicycle while quite unconscious of any intention to remain upright and balanced on the bike. So, as in a number of these notes on words, we need to observe a caution: we should never ascribe our own sort of consciousness to other organisms, who seem to function quite well by means of intentions that do not originate in (their own) conscious or self-aware activity.

Interiority. See Theme #2 above.

Material. Accessible through our senses.

Material/physical/materialist. I speak broadly of “the material world” as the world we routinely experience, the world we live and move in. “Material” and “physical” might be taken as rough synonyms, but I preferentially use “material” when speaking about the sensible world as we actually know it, and I use “physical” when emphasizing the habits of thought that come to the fore when, as *materialists*, we are thinking theoretically about the nature of the world and trying to conceive it purely in terms of physical entities and processes conceived as mindless and having nothing to do with our own interiority. So I might say on one hand that the organism adapts to its *material* environment, but, on the other hand, that we are commonly thought to live in a world subject only to *physical* laws. But there is no strict line between these terms, and doubtless no full consistency in my usage. Problems arise because the idea of the physical is incoherent: physical laws are ideal and conceptual, not mindless and physical in the sense of “physical” usually taken for granted.

Meaning. All coherent descriptive content is meaningful, a fact already implicit in the word “coherent”. Meaning seems to us problematic only because we have culturally inherited materialist mindsets, and because meaning is so thoroughly inescapable that we have a hard time stepping back and seeing it for what it is. The sea of meaning is that from which we are born and in terms of which we continue to live and finally die. We cannot do anything or say anything or pursue any science without the doing, saying, or pursuing being an expression of meaning.

Some people have a very difficult time with any use of the word “meaning” in a scientific context. It’s worth setting this difficulty alongside the simple fact that the only things we *know* about the world are meanings. The idea that we are dealing with genuine meaning, not meaninglessness, is already implicit in the word “know”. Meaninglessness would not yield itself to knowing articulation, as in science. Meaning cannot be questioned. The effort to question or define it — or just point to it — assumes that the person being addressed already possesses a working understanding of meaning, such as the meaning of a pointing finger. Acting out meanings is pretty much the only thing we do with our lives. The same thing is true of organisms generally, all the way down to one-celled creatures — except that they lack the capacity for conscious awareness of the meanings at work in their lives. The interesting question has to do with the *different* meanings at work in different kinds of organism.

The fact that we are dealing with the fundamental basis of life when we use this term is hardly a reason to avoid it in biology. The (always unsuccessful) effort of avoidance is perhaps the central pathology of contemporary biological thought and practice. In a thousand ways the taboo against any suggestion of meaningfulness makes a fool of scientists and nonsense of their language.

Narrative. See Theme #1 above.

***Telos*-realizing.** *Telos* (“end”) is often taken to refer to final causation — to the *end* we humans are aiming at when we formulate plans. But, consistent with the Greek term, it may be more useful to take the “end” as a matter of *self-realization*, which is the “being at work remaining oneself” referred to under “Integral unity of the organism” above. Or, we might say, “being oneself ever differently”. It’s a matter of bringing what one is to ever fuller expression — taking always a further (new) step in expressing one’s own nature. Only in the human case does this involve a creative awareness whereby an action becomes intimately *our own*.

Regarding the ideas conveyed by “end”, “self-realization”, and “holism”, we have this incisive comment by the philosopher Ronald Brady: An organism’s biological development “does not proceed towards [a] whole, but rather *expresses* it” (Brady 1987). It is, however, hard to find words that capture the meaningful coordination of processes in the achievement of a certain result without seeming to imply an external goal, so ambiguity will doubtless remain. The alert reader will need to make an inner adjustment whenever encountering language that sounds external-goal-directed.

See also the word “directive” above.

Where is the evidence? Two concluding notes

The preceding discussion, especially that of Themes #1 and #2, underscores a truth that is alien to contemporary biology: *We meet in the living world something akin to our own inner being.* Everything I have hinted at here, however, desperately needs expansion, which is why this book was written.

But while the themes and underlying convictions shaping the character of the book lie far outside mainstream thinking, I offer no new or revolutionary findings in biology or evolutionary theory — and would lack the qualifications for doing so even if that were my inclination. Instead, I merely ask: What would biology and evolutionary theory look like if we overcame our blindsight and reckoned with the stories of organisms as we actually observed them? Can we allow ourselves to see with restored vision?

And so there will be no occasion for readers to ask, “Where is all the new evidence?” The evidence supporting my contentions here — as I try to show chapter by chapter — amounts to just about *everything* biologists have already recognized as truth, however much they might prefer not to acknowledge the gifts of their own insight. This is why you will not find me straining toward the fringes of biology, but rather citing, with very few exceptions, one fully accredited researcher and theorist after another. The case for a thoroughly disruptive re-thinking of organisms and their evolution has long been staring us in the face.

A second note is not unrelated to the first. Throughout this book I have, to a degree, tuned my vocabulary to the more complex animals with which we are most familiar, although the language could readily be adjusted to reflect the intelligent life processes in bacteria, plants, and other groups. Many will say that this is to ignore what are by far the most abundant creatures on earth. Perhaps so. But I am convinced that, contrary to the usual intuitions, the “higher” organisms are key to understanding the “lower”, not the reverse.

This is true in the indisputable sense that the kind of understanding we are looking for emerges only in humans, so that we are the *only* means for understanding other creatures. But I believe it is also true in the sense that those organisms more fully manifesting the potentials of life do in fact *more fully manifest the potentials of life*.

At the same time, we have no reason to think that the intelligence working through the material limitations of, say, bacteria is a “lower” or less capable intelligence than that which is at work in ourselves — or that the intelligence at work in our cells is lower than what works in our conscious minds. Actually, our cellular intelligence quite evidently far transcends our conscious capacities. We can say this without doubting that the arrival of a self-aware sort of consciousness is a pivotal development in the evolution of life. It’s just that we have no grounds for arrogance regarding our current conscious achievements. These achievements are, in the overall context of life on earth, humble indeed!

Notes

1. Figure 1.1 credit: Rama Warrier (CC BY-SA 4.0).

2. Figure 1.2 credit: Pollinator (CC BY-SA 3.0)

Sources

Brady, Ronald H. (1987). “Form and Cause in Goethe’s Morphology”, in *Goethe and the Sciences: A Reappraisal*, edited by F. Amrine, F. J. Zucker, and H. Wheeler, pp. 257-300. Dordrecht, Holland: D. Reidel. Available on the Nature Institute’s website: https://natureinstitute.org/ronald-h-brady/form-and-cause-in-goethes-morphology

Lewontin, Richard (2000). *The Triple Helix: Gene, Organism, and Environment*. Cambridge MA: Harvard University Press.

March, Robert (1977). *Physics for Poets*. Chicago: Contemporary Books.

Oyama, Susan (2000). *The Ontogeny of Information*, 2nd edition, foreword by Richard C. Lewontin. Durham NC: Duke University Press. First edition published in 1985 by Cambridge University Press.

Russell, E. S. (1945). *The Directiveness of Organic Activities*. Cambridge UK: Cambridge University Press.

Sachs, Joe (1998). *Aristotle’s Physics: A Guided Study*. New Brunswick NJ: Rutgers University Press. Originally published in 1995.

Watson, E. L. Grant (1964). *The Mystery of Physical Life*. Hudson NY: Lindisfarne Press. Originally published in 1943.

Welburn, Andrew (2004). *Rudolf Steiner’s Philosophy — And the Crisis of Contemporary Thought*. Edinburgh UK: Floris Books.

CHAPTER 2

The Organism's Story

Organisms are purposive ("teleological") beings. Nothing could be more obvious. The fact of the matter is so indisputable that even those who don't believe it really do believe it. Philosopher of biology Robert Arp speaks for biology as a whole when he writes,

> Thinkers cannot seem to get around [evolutionary biologist Robert] Trivers' claim that "even the humblest creature, say, a virus, appears organized to *do* something; it acts as if it is trying to achieve some purpose", or [political philosopher Larry] Arnhart's observation that … "Reproduction, growth, feeding, healing, courtship, parental care for the young — these and many other activities of organisms are goal-directed".[1]

And yet, despite his acknowledgment that we "cannot get around" this truth, Arp again speaks for almost the entire discipline of biology when he tries, with some delicacy, to get around it: "with respect to organisms, it is useful to think *as if* these entities have traits and processes that function in goal-directed ways".[2] This *as if* is a long-running cliché in biology, designed to warn us that the organism's purposive behavior is somehow deceptive — not quite what it seems. The goal-directedness is, in the conventional terminology, merely *apparent* or *illusory*. Certainly it must not be seen as having any relation at all to human purposive activity — an odd insistence given how eager so many biologists are to make sure we never forget that the human being is "just another animal".

Others have commented on this strange, blindsighted reluctance to acknowledge fully the purposiveness that is there for all to see. The philosopher of science, Karl Popper, said that "The fear of using teleological terms reminds me of the Victorian fear of speaking about sex".[3] Popper may have had in mind a famous remark by his friend and twentieth-century British evolutionary theorist, J. B. S. Haldane, who once quipped that "Teleology is like a mistress to a biologist; he cannot live without her but he's unwilling to be seen with her in public".[4]

We find this same unwilling yet unshakable conviction of purposiveness at the foundations of evolutionary theory. The theory, we are often told, is supposed to explain away the organism's purposes — "naturalize" them, as those who claim to speak for nature like to say. But at the same time the theory is itself said to be grounded solidly in the fact that organisms, unlike rocks, thunderstorms, and solar systems, *struggle to survive and reproduce*. If they did not spend their entire lives striving toward an end, or *telos*, in this way, natural selection of the fittest organisms (those best qualified to survive and reproduce) could not occur. So it is not at all clear how selection is supposed to explain the origin of such end-directed behavior.

A double and conflicted stance toward end-directedness — believing and not believing, acknowledging and explaining away — constitutes, you could almost say, the warp and woof of biology itself. Look for "purpose" in the index of any biological textbook, and you will almost certainly be disappointed. That term, along with others such as "meaning" and "value", is effectively banned. There is something like a taboo against it.

Yet, in striking self-contradiction, those textbooks are themselves structured according to the purposive activities and meaningful tasks of organisms. Biologists are always working to narrate goal-directed achievements. How is DNA replicated? How do cells divide? How does metabolism supply energy for living activity? How are circadian rhythms established and maintained? How do animals arrive at the evolutionary strategies or games or arms races through which they try to eat and avoid being eaten?

Such questions are endless, and their defining role is reflected on every page of every textbook on development, physiology, behavior, or evolution. A research question is *biological*, as opposed to physical or chemical, only when it is posed in one way or another by the organism's purposive, future-oriented activity. The puzzle is that, having been aroused by such purposive questions, biologists look for answers rooted in the assumption that organisms have no purposes. The reigning conviction is that explanations of physical and chemical *means* effectively remove any need to deal scientifically with the *ends* that alone could have prompted our search for means in the first place.

My larger argument in this book will be that the biologist's conscious commitment to purely physical and chemical descriptions — which is to say, her conscious refusal of much that she actually knows — has devastating effects upon many fields of biological understanding, and particularly evolutionary theory. It hardly needs emphasizing that *if* organisms really are purposive beings — if the fact of purposive activity is not an illusion — then a biological science so repulsed by the idea of purpose that its practitioners must avert their eyes at the very mention of it … well, it appears that these practitioners must feel threatened at a place they consider foundational. And with some justification, for to admit what they actually know about organisms would be to turn upside down and inside out much of the science to which they have committed their lives.

"Purpose" — an idea that will need careful qualification in different biological contexts — gives us but one of several intimately related avenues of approach to what is distinctive about the life of organisms. In the remainder of this chapter I will briefly sketch a few of these avenues.

Organisms are agents capable of expressing their own meanings

Organisms are agents; they *do* things. The difference between a motionless rock, on one hand, and a motionless cat on the other is that the cat is not merely motionless; it is *resting*, or perhaps preparing to pounce. When it ceases *doing* things, it is no longer alive. Whereas a rock may *be moved* by impinging forces, the cat itself *moves*. In our routine experience we take self-motivated activity to be definitive of living things. If an object moves unexpectedly — without an evident external cause — we immediately begin testing the assumption that it is living.

When an animal responds to a physical stimulus, its response is not in any strict way physically enforced, or directly caused, by the stimulus. Rather, the animal “reads” the meaning of the situation in light of its own concerns, including its needs and interests, and then alters that meaning by responding to it. If the animal *is* physically moved by a stimulus, as when a rolling stone bumps into a leg, we don’t consider the movement to be the organism’s own act. It is not a *response*, but merely a physically caused *result*.

As a useful picture of this, we need only consider how the negligible force producing an image on the retina — say, the image of a charging lion — can set the entire mass of a quarter-ton wildebeest into thundering motion. The impelling force comes from within, so that the movement seems to originate within the animal itself in a way that we do not see in inanimate objects.

Figure 2.1. A wildebeest, otherwise known as a gnu.[5]

The wildebeest is not forcibly moved by a physical impact, but rather *perceives* something. Further, its perception is at the same time an *interpretation* of its surroundings from its own point of view and in light of its own world of meaning. The “lawfulness” at issue here, such as it is, is far from being universal. It differs radically from one living being to another, so that the retinal image of a charging lion means a very different thing to the wildebeest from what it means to another lion or to a vulture circling overhead. And it produces an altogether different response in these cases.

Figure 2.2. A charging lioness in the Serengeti.[6]

All this may seem trivially obvious — and so it is. We make sense of biological activity in terms of meanings radically different from the meanings we bring to inanimate events. But this only renders more poignant biologists’ futile desire to pursue their *explanatory* tasks as if there were no such radical distinction between the animate and inanimate.

Nevertheless, we all find it difficult to conceal or deny what we know. So despite the biologist’s attempted disavowal of what is distinctively biological in her science, the truth comes out in a thousand ways, and above all in the choice of language. The words employed for description of animate activity differ dramatically from those applied to inanimate activity.

Think, for example, of a living dog, then of its 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 inanimate nature as the live dog. But now, with the cessation of life, we see those laws strictly in their own terms, without reference to life. The dramatic change in our descriptive language as we move between the living and the dead speaks more loudly than any philosophical convictions we may have about life and death.

No biologist who had been studying the *behavior* of the living dog will concern herself with the corpse's "behavior". Nor will she refer to certain physical changes in the corpse as *reflexes*, just as she 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. No structures will *inherit* features from parent structures in the way that daughter cells inherit traits or tendencies from their parent cells, and no one will cite the *plasticity* or *context-dependence* of the corpse's *adaptation* to its environment.

The language highlighted here is clearly a language of more-than-physical meaning. When investigators do their best to ignore these additional layers of meaning — for example, when they present their findings *as if* they were merely elucidating physical and chemical interactions — then they are contradicting just about all their own biological descriptions.

It is not that conventional approaches are inadequate in their own, limited terms. *In such terms* we can be sure that everything being described makes perfect sense, and that the physical picture reveals no mysterious gaps. It's just that, within the arbitrarily imposed limits of physical and chemical description, we will see no living activity. "Physically lawful" describes only those aspects of the animal's body that continue uninterrupted, according to exactly the same laws, when it dies. If we restricted our understanding to *this* characterization, death would not even be a recognizable event.

Of course, in a split-personality, blindsighted sort of way every biologist does recognize death, because she recognizes the distinctive sorts of meaning, including the perceptions, purposes, intentions, and responses, that the once-living dog is no longer expressing. It's just that she typically refuses to let the expressive aspects of the creature's life become uncomfortably explicit, or to influence fundamental theory. Or, when they do affect theory, it must be the organism's physical activity, not its interior life as a perceptive and intentional actor, that enters into scientific consideration. Like the behaviorists of old, we are forbidden to accept the inner, immaterial, and immediately given *reality* of perceptions and intentions, as opposed to various associated physical manifestations.

The end is more constant than the means of attaining it

William McDougall, who lived from 1871 to 1938, was a highly respected (if also rather controversial) British psychologist who, after teaching at Oxford, spent the latter part of his career in the United States. He authored widely used textbooks of psychology and, for several years, occupied William James' chair at Harvard. Then he moved to Duke University where, with J. B. Rhine, he founded the Parapsychology Laboratory. Our present interest, however, is in a 1929 work, where McDougall usefully summarized certain typical features of purposive activity (McDougall 1929, pp. 50-51). He was writing about human behavior, but we can recognize something like these features in all purposive behavior, conscious or otherwise:

- Goal-directed activity tends to be *persistent* and may be repeatedly renewed even after being effectively blocked for a time. If you tie up your hungry dog at some distance from its food bowl, it may cease straining at the leash. But as soon as you grant it freedom, it will again head for the bowl.
- Goal-directed activity is very often *adaptable* to one degree or another. If one strategy fails, the organism may vary it or switch to a different strategy. As many dog owners have discovered after forgetting to give Fido his food, their beloved pet may contrive to enjoy the freshly roasted chicken on the kitchen counter.
- And, as soon as the goal is reached, that particular goal-directed activity *ceases*. Having had its fill, your dog may want to play or else to sleep. But it will not continue its quest for food.

We do not find the same combination of features in the inanimate world. Yet anyone who interacts with animals takes them for granted. Moreover, analogous features are evident even in physiological activity, all the way down to the molecular biology of the cell. In its development "the embryo seems to be resolved to acquire a certain form and structure, and to be capable of overcoming very great obstacles placed in its path". When encountering such an obstacle to its development, the organism "adjusts itself to the changed conditions, and, in virtue of some obscure directive power, sets itself once more upon the road to its goal; which under the altered conditions it achieves only by means of steps that are different, sometimes extremely different, from the normal" (McDougall 1911, pp. 242-43).

When a cell is preparing to divide, it passes through what are known as internal "checkpoints", where the cell responds to the presence or absence of conditions necessary for a successful division. If something is awry, the cell may *persist* in the aim of dividing by taking any corrective (*adaptive*) action that happens to be within its power. It then proceeds with its division, and *ceases* the entire, highly coordinated and complex activity once the process is complete. (And when division is inadvisable — say, because chromosomes have been irreversibly damaged too badly — the cell may proceed toward a larger end, whereby its distinct existence ceases and its resources are offered up to the rest of the organism of which it is a part.)

No one will bristle upon hearing that “this cell is preparing to divide”. But we would certainly bristle if we heard that “Mars is preparing to make another journey around the sun”, or “the nebula has ceased its effort after forming the solar system”. A planet moves according to universal laws acting in an unchanging manner. There is no point in its journey when an act is *initiated* or *concluded*, but only the playing out of the immediately preceding forces. There is in this sense nothing new to explain. Biological explanation, by contrast, always involves something new, an element of initiative, a response to circumstances not fully necessitated by the preceding play of physical and chemical processes.

Here’s another illustration, drawn from the great English physiologist, Sir Charles Scott Sherrington, writing in 1922. He is talking about what happens when, in some animals, a motor nerve is severed and the portion running from the point of severance to the muscle dies. The living end of the nerve immediately embarks upon a meaningful and unfathomably complex journey:

> The fibre, so to say, tries to grow out to reach to its old far-distant muscle. There are difficulties in its way. A multitude of non-nervous repair cells growing in the wound spin scar tissue across the new fibre’s path. Between these alien cells the new nerve-fibre threads a tortuous way, avoiding and never joining any of them. This obstruction it may take many days to traverse. Then it reaches a region where the sheath-cells of the old dead nerve-fibres lie altered beyond ordinary recognition. But the growing fibre recognises them. Tunnelling through endless chains of them, it arrives finally, after weeks or months, at the wasted muscle-fibres which seem to have been its goal, for it connects with them at once. It pierces their covering membranes and re-forms with their substance junctions of characteristic pattern resembling the original that had died weeks or months before. Then its growth ceases, abruptly, as it began, and the wasted muscle recovers and the lost function is restored (Quoted in Russell 1945, p.111).

Here we see again goal-directed persistence over a long period, adaptability in the face of obstacles, and cessation of this particular activity when its end is achieved.

Notice also Sherrington’s careful caveat (“so to say”) whereby he qualifies the easily anthropomorphized phrase, “*tries* to grow”. The care and the qualification are fully justified. But the fact is that such phrasing is pervasive and seemingly unavoidable whenever the researcher would offer informative biological descriptions. This suggests that we owe it to the discipline of biology to explore the nature of our own usage. It pays to know what we are *really* saying, rather than leaving it in a vague and ambiguous cloud of suggestion. Throughout this book we will touch on some of the problems we run into when employing the easily misused language of purposiveness, goals, and intentions.

E. S. Russell, a British marine biologist whose writings during the first half of the twentieth century can sometimes seem more up-to-date regarding the decisive issues of twenty-first century biology than the literature of our own day, summarized the gist of the foregoing discussion with wonderful succinctness: “The end-state is more constant than the method of reaching it” (Russell 1945, p. 110). This suggests that the end-state, understood as somehow implicit in the entire drama leading up to it, plays something like a causal role. It reminds one of the way a well-considered conclusion is implicit in the profound, multivalent play of thought leading up to it, rather than being the mere passive outcome of a deterministic march of machine logic. (For a fuller treatment of this, see the section on leaf sequences in Chapter 12 ("Is a Qualitative Biology Possible?").

Surely any such causal dimensions involving end-states would have large implications for a science determined to unravel physical and chemical means while pretending to ignore the ends that express the meaning of the activity.

Every organism is narrating a meaningful life story

The fact of purposive activity; the obvious play of an active agency; the coordination of diverse means toward the realization of countless interwoven and relatively stable ends; the undeniable evidence that animals perceive a world, interpreting and responding to perceptions according to their own way of life; and the coherence of all this activity in a governing unity — this tells us that every organism is narrating a meaningful life story. This is not something that a rock, say, loosened by ice and tumbling down the steep slope of a mountain ravine, does in anything like the same manner. The pattern of physical events in the organism is raised by its peculiar sort of coherence toward something like a biography whose "logic" unfolds on an entirely different level from the logic of inanimate physical causation. When we tell a story, the narrative threads convey the meanings of a life — for example, motives, needs, and intentions — and these are never a matter of mere physical cause and consequence.

So when I speak of the organism's wise and knowing agency, or its purposive striving, I refer, among other things, to *its capacity to weave, out of the resources of its own life, the kind of biological narrative we routinely observe, with its orchestration of physical events in the service of the organism's own meanings*.

We normally feel every birth as a new beginning, full of hope and expectation — a beginning of a sort we do not experience in the genesis of a raindrop or dust devil. Even the first shoot of a bean or squash seed, pushing upward through the soil surface, is the prelude to a narrative promising many vicissitudes — engagements with insects and diseases, complex communal relations with other plants, and confrontations with nurturing or threatening forces of nature. And a death is always the end of one particular story.

E. S. Russell, commenting on descriptions such as those of the chaffinch in Box 2.1, noted the narrative connectedness of the events: "Behaviour is often part of a long-range cycle of events, in which one action prepares for and leads on to the next until the end term is reached. Each stage in the chain or cycle is unintelligible to us except in its relation to what has gone before, and, more particularly, to what is yet to come. Such cycles have a temporal unity …" (Russell 1938, pp. 7-8). Present significances are interwoven with and inseparable from the tapestry of past events and their meanings. And future developments, along with whatever new and unpredictable elements they bring, are a continued, improvisational elaboration of the same tapestry of meaning.

In other words, the "end" being approached in an organism's story is not some particular, discrete accomplishment, distinct from the means of getting there, but rather the wholeness and perfection of the entire narrative movement from "here" to "there". Assessing this end is much the same as if we were assessing the meaning of a novel: knowing the ending in isolation would have little significance compared to knowing the larger story of which,

Box 2.1

The Nesting Cycle of the Chaffinch

From a 1927 description by the British naturalist and ornithologist, Edward Max Nicholson:[7]

"The male must leave the flock, if he has belonged to one, and establish himself in a territory which may at the time be incapable of sustaining him alone, but must later in the season supply a satisfactory food-supply for himself, his mate and family, and for as many birds of other species as overlap his sphere of influence. He must then sing loudly and incessantly for several months, since, however soon he secures a mate, trespassers must be warned off the territory, or, if they ignore his warning, driven out.

"His mate must help with the defence of the territory when she is needed; pairing must be accomplished; a suitable site must be found for the nest; materials must be collected and put together securely enough to hold five bulky young birds; eggs must be laid in the nest and continuously brooded for a fortnight till they hatch, often in very adverse weather; the young are at first so delicate that they have to be brooded and encouraged to sleep a great part of the time, yet they must have their own weight of food in a day, and in proportion as the need of brooding them decreases, their appetites grow, until in the end the parents are feeding four or five helpless birds equal to themselves in size and appetite but incapable of digesting nearly such a wide diet.

"Enemies must be watched for and the nest defended and kept clean. When the young scatter, often before they can fly properly, they need even greater vigilance, but within a few days of the fledging of the first brood a second nest will (in many cases) be ready and the process in full swing over again. All this so we often feel, it is a necessary and proper part.

has to be done in face of great practical difficulties by two creatures, with little strength and not much intelligence, both of whom may have been hatched only the season before.”

We are organisms, but not all organisms are human

Note well, then, that when speaking of the organism’s story, we need make no reference to the consciously directed performances of human beings, even though our performances certainly exhibit a narrative character in the sense meant here. When I refer to living activity as “end-directed”, I am not suggesting the formulation of a conscious goal that is “aimed at”. I mean, rather, something like this:

> The organism’s life is a continual *playing forward of meanings within meaningful contexts*. There is a certain directedness to any such play of meaning (as when birds build a nest), but it need not be the directedness of human plan fulfillment.

The directedness of a temporally unfolding play of meaning implies no narrow goal and no conscious planning. But every such play of meaning does have a certain directedness to it. Think of the greatest poems or novels, where nothing is calculated *in order to* reach the conclusion, but the movement is nevertheless from the beginning to the end, not the reverse. This movement simply expresses the progressive deepening of a meaningful and coherent unity — more like a dance than pursuit of a fixed and predefined goal. And the dance looks ever more improvisational as organisms ascend in the scale of complexity.

I offer no specific hypotheses to explain the existence of intentional agency and story narration. I only note that the *fact* of the narrative is immediately demonstrable in every organism. There may be huge differences in the nature of the stories that can be told by different kinds of organism, but from the molecular level on up there are always elements of story that we do not find in inanimate things. The narrative of meaningful activity undertaken and accomplished is there to be seen, and is characterized as such, if only inadvertently, in every paragraph of biological description.

Moreover, our recognition of intelligent and intentional activity does not require us to understand its source. Looking at the pages of a book, we have no difficulty distinguishing written marks from deposits of lint and dust, even if we know nothing about the origin of the marks. We can declare a functioning machine to be engaged in a purposive operation, whether or not we have any clue about the engineers who built a mechanistic reflection of their own purposes into it. And if we find live, intelligent performances by organisms, we don’t have to know how, or from where, the intelligence gets its foothold before we accept the testimony of our eyes and understanding.

Neither should we expect the stories to be predictable — no more than we expect the ending of a half-read novel to be predictable. We can, however, expect the ending to *make* *sense*, and even to throw light on everything that went before. The story will *hold together* in a way that unstoried physical events do not.

The storytelling is the being of the organism

If the organism's life is an unfolding story, then we might well take the essence of that life to be the *storytelling* itself, not the particular embodiment of the story at any frozen instant. Organisms, as philosopher Hans Jonas has written, "are individuals whose being is their own doing … they are committed to keeping up this being by ever renewed acts of it." Their identity is "not the inert one of a permanent substratum, but the self-created one of continuous performance" (Jonas 1968, p. 236, 233).

Or, again, we have the rather different formulation by Paul Weiss, a National Medal of Science recipient and profound observer of cellular life:

> 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 (Weiss 1962, p. 3).

An organism is not, most essentially, its body. After all, its body at one time is never materially identical to its body at a different time. It is, rather, a unique power of activity. Its body is first of all a result of this activity, while also developing into a further vehicle for it. Organisms, in other words, are *doings* rather than *beings*. Or, as the student of holistic thinking, Henri Bortoft, has put it, they are "doings that be", not "beings that do".[8]

So it is not that an organism's material being determines its doings (as is broadly assumed throughout the biological sciences); rather, its doings are what constitute it as a material being. This means that it is never wholly present to our observation in any outward or material sense. The organism's essential power to act cannot itself be a visible product of its activity.

The preeminence of activity in relation to physical substance and structure would, if taken seriously, give us an altogether new science of life. For example, it might have saved us from an entire century of badly misdirected thinking about DNA and genes. It might also have spared biologists the crude materialism that many physicists long ago gained the freedom to question.

But this is to get ahead of the story. For now, it is enough to mention two questions implicit in the foregoing, while deferring further comment:

Regarding our theory of evolution: If, in reality, every organism's existence is a live, moment-by-moment, improvisational storytelling — a creative and adaptive, irreversible narrative that is always progressing coherently and contextually from challenge to response and adaptation, from initiative to outcome, from nascence to renascence, from immaturity through maturity to regeneration — then an evolutionary theory rooted in notions of random variation and mindlessness is a theory hanging upon a great question mark. "The answer to the question of what status teleology ['end-directedness'] should have in biology" — so the influential biologist and philosopher Francisco Varela came to see at the end of his life — determines “the character of our whole theory of animate nature” (Weber and Varela 2002).

And then there is the question whether the future of individual species, the future of particular ecological settings, the future of life’s diversity on earth, and the future of earth itself, all depend on our willingness and ability to attend to the life stories of the beings among whom we live — depend, finally, on our capacity for the reverence that these stories so naturally evoke.

WHERE ARE WE NOW?

An organism’s story gives form to its material existence (not the other way around)

We have seen that animals are irreducibly purposive, from their behavior to their physiology, and that the ends being sought are more constant than the means for seeking them. We have also seen that animals are moved by perceived meanings rather than impelling physical forces.

There are many issues raised by the discussion in this chapter, including these:

- Given that we share common roots with all life, what is the relation between the purposes of organisms in general and our own human purposes?
- Does saying that the organism makes a story of its life imply a form of consciousness?
- Do not the cells of our own bodies (and of other organisms) manifest something of a narrative character in their own right — or at least actively *participate* in, or ably play their roles within, our larger narratives?
- How do our own human purposes relate to the purposiveness in our bodies and cells, through which many of our intentions are carried out?

And much more. Many chapters in this book will feed into at least tentative answers to these questions. And at times — such as in Chapters 24 and 25 — we will face the issues head on. You will also find some helpful preliminary notes in Chapter 1.

Notes

1. Arp 2007. See also Trivers 1985, p. 5. In this same connection, the following comment by Georg Toepfer of Humboldt University in Berlin is significant:

> Most biological objects do not even exist as definite entities apart from the teleological perspective. This is because biological systems are not given as definite amounts of matter or structures with a certain form. They instead persist as functionally integrated entities while their matter and form changes. The period of existence of an organism is not

> determined by the conservation of its matter or form, but by the preservation of the cycle of its activities (Toepfer 2012).

Then there is this from the American philosopher, Susanne Langer:

> The image of life as motivated activity reflects an aspect of animate nature that has baffled philosophers ever since physics rose to its supreme place among the sciences, because inanimate nature — by far the greatest concern of physics — has no such aspect: the telic phenomenon, the functional relation of needs and satisfactions, ends and their attainment, effort and success or failure. There are no failures among the stars. Rocks have no interests. The oceans roar for nothing. But earthworms eat that they may live, and draw themselves into the earth to escape robins, and seek other worms to mate and procreate. They need not know why they eat, contract, or mate. Their acts are telic without being purposive (Langer 1967, p. 220).

But, of course, "telic" just means "purposive". What I think she is getting at is that purposive or end-directed activity need not be *consciously* purposive — that is, need not be *planned*.

[2]. Emphasis in original. Hereafter and in all succeeding chapters this can be assumed unless explicitly stated otherwise.

[3]. Quoted in Niemann 2014, p. 30.

[4]. Quoted in Mayr 1974. Reports of this remark by Haldane come with many variations. The eminent French biologist, François Jacob, wrote, without attribution: "For a long time, the biologist treated teleology as he would a woman he could not do without, but did not care to be seen with in public" (Jacob 1973, pp. 8-9).

[5]. Figure 2.1 credit: Wildebeest photo by Chris Eason (CC BY 2.0).

[6]. Figure 2.2 credit: Lion photo by Schuyler Shepherd (CC BY-SA 2.5).

[7]. Quoted in Russell 1938, pp. 7-8. I have added paragraph breaks. The book by Nicholson is entitled *How Birds Live: A Brief Account of Bird-Life in the Light of Modern Observation*, and was published in London by Williams and Norgate, Ltd., in 1927.

The engraving of a chaffinch pair and their nest is from a book published in 1866 and titled, *Homes Without Hands: Being a Description of the Habitations of Animals, Classed According to Their Principle of Construction*, by John George Wood and others. For more information, see The Internet Archive Book Images.

[8]. The idea is central to the work of Bortoft, who ascribes this particular (apparently unpublished) formulation to the British scientist and philosopher, J. G. Bennett. See Bortoft 1996, p. 270.

Sources

Arp, Robert (2007). “Evolution and Two Popular Proposals for the Definition of Function”, *Journal for General Philosophy of Science* vol. 38, pp. 19-30. doi:10.1007/s10838-006-9008-3

Bortoft, Henri (1996). *The Wholeness of Nature: Goethe’s Way toward a Science of Conscious Participation in Nature*. Hudson NY: Lindisfarne.

Jacob, François (1973). *The Logic of Life: A History of Heredity*, translated by Betty E. Spillmann. New York: Random House. Originally published in French in 1970.

Jonas, Hans (1968). “Biological Foundations of Individuality”, *International Philosophical Quarterly* vol. 8, no. 2, pp. 231-51.

Langer, Susanne K. (1967). *Mind: An Essay on Human Feeling* vol. 1. Baltimore MD: Johns Hopkins University Press.

Mayr, Ernst (1974). “Teleological and Teleonomic, a New Analysis”, in *Methodological and Historical Essays in the Natural and Social Sciences* (vol. 14 of Boston Studies in the Philosophy of Science), edited by Robert S. Cohen and Marx W. Wartofsky. Dordrecht, Holland: Springer Netherlands, pp. 91-117. doi:10.1007/978-94-010-2128-9_6

McDougall, William (1911). *Body and Mind: A History and a Defense of Animism*. New York: Macmillan.

McDougall, William (1929). *Modern Materialism and Emergent Evolution*. New York: D. Van Nostrand.

Niemann, Hans-Joachim (2014). *Karl Popper and the Two New Secrets of Life*. Tübingen, Germany: Mohr Siebeck.

Russell, E. S. (1938). *The Behaviour of Animals*, second edition. London: Edward Arnold.

Russell, E. S. (1945). *The Directiveness of Organic Activities*. Cambridge UK: Cambridge University Press.

Toepfer, Georg (2012). “Teleology and Its Constitutive Role for Biology as the Science of Organized Systems in Nature”, *Studies in History and Philosophy of Biological and Biomedical Sciences* vol. 43, pp. 113-19. doi:10.1016/j.shpsc.2011.05.010

Trivers, Robert (1985). *Social Evolution*. Menlo Park CA: Benjamin-Cummings.

Weber, Andreas and Francisco J. Varela (2002). “Life after Kant: Natural Purposes and the Autopoietic Foundations of Biological Individuality”, *Phenomenology and the Cognitive Sciences* vol. 1, pp. 97-125. Available at https://link.springer.com/article/10.1023/a:1020368120174

Weiss, Paul (1962). “From Cell to Molecule”, in *The Molecular Control of Cellular Activity*, edited by John M. Allen, pp. 1-72. The University of Michigan Institute of Science and Technology Series. New York: McGraw-Hill.

Chapter 3

What Brings Our Genome Alive?

Throughout most of the twentieth century, genes were viewed as the “agents” responsible for an organism’s development, activity, and evolution. Their agency was said to lie in their ability to “regulate”, “organize”, “coordinate”, and “control” physiological processes. DNA, the bearer of these genes, became the “Book of Life” — the essential maker of organisms and driver of evolution. And this view remains stubbornly entrenched today, despite many changes in our understanding. A leading behavioral geneticist has recently written a book entitled, *Blueprint: How DNA Makes Us Who We Are*.

Nevertheless, the idea that genes are the decisive “first causes” of life — and, more generally, that molecules at the “bottom” ultimately explain everything that happens at larger scales — has come in for a great deal of criticism in recent years. This criticism, as we will see, is fully justified. But the issues can be subtle, as is suggested by an apparent paradox. Philosopher of biology Lenny Moss, who wrote the valuable book, *What Genes Can’t Do*, has remarked:

> Where molecular biology once taught us that life is more about the interplay of molecules than we might have previously imagined, molecular biology is now beginning to reveal the extent to which macromolecules [such as DNA], with their surprisingly flexible and adaptive complex behavior, turn out to be more *life-like* than we had previously imagined (Moss 2012).

In a similar vein, I myself wrote a decade ago:

> Having plunged headlong toward the micro and molecular in their drive to reduce the living to the inanimate, biologists now find unapologetic life staring back at them from every chromatogram, every electron micrograph, every gene expression profile. Things do not become simpler, less organic, less animate. The explanatory task at the bottom is essentially the same as what we faced higher up (Talbott 2010).

But if all this is true, what are we to make of Harvard geneticist Richard Lewontin’s declaration, itself hardly disputable, that

> DNA is a dead molecule, among the most nonreactive, chemically inert molecules in the living world. That is why it can be recovered in good enough shape to determine its sequence from mummies, from mastodons frozen tens of thousands of years ago, and even, under the right circumstances, from twenty-million-year-old fossil plants … DNA has no power to reproduce itself. Rather it is produced out of elementary materials by a complex cellular machinery of proteins. While it is often said that DNA produces proteins, in fact proteins (enzymes) produce DNA … Not only is DNA incapable of making copies of itself, aided or unaided, but it is incapable of “making” anything else (Lewontin 1992).

Many astute observers have echoed Lewontin’s remarks, and I have never seen anyone question them, including those who remain enamored of the “Book of Life”. So which is it? When we peer at DNA, do we see a dead molecule or the secret of life? As it happens, there is a simple answer: if we are looking at a molecule conceived in the usual way as a bit of mindless, inherently inert stuff, then, according to our own conceptions, we see only dead stuff. But if we observe the molecule as a system of forces and energies capable of *participating and being caught up in* the creative life of the whole cell and organism, then we can hardly help recognizing — and perhaps even reverencing — the living performance unfolding before our eyes.

Saying this is one thing; making it both meaningful and profound is quite another — and that is one task of the present book. So let us begin.

The genome as you have probably not heard about it

If you arranged the DNA in a human cell linearly, it would extend for nearly two meters. How do you pack all that DNA into a cell nucleus just five or ten millionths of a meter in diameter? According to the usual comparison it's as if you had to cram twenty-four miles (forty kilometers) of extremely thin thread into a tennis ball. Moreover, this thread is divided into forty-six pieces (individual chromosomes) averaging, in our tennis-ball analogy, over half a mile long. Can it be at all possible not only to fit those chromosomes in the nucleus, but also to keep them from becoming hopelessly entangled?

Obviously it must be possible, however difficult to conceive. The first thing to realize is that chromosomes do not consist of naked DNA. Their actual substance, an intricately woven and ever-changing structure of DNA, RNA, and protein, is referred to as *chromatin*. (See Box 3.1 for some basic terminology.) Histone proteins, several of which can bind together in the form of a complex *histone core particle*, are the single most prominent, non-DNA constituents of this chromatin. Every cell contains numerous such core particles — there are some 30 million in a typical human cell — and the DNA double helix, after wrapping a couple of times around one of them, typically extends for a short stretch and then wraps around another one. The core particle with its DNA wrapping is referred to as a *nucleosome* (about which you can read much more in Chapter 14), and between 75 and 90 percent of our DNA is wrapped around nucleosomes. This is one way the cell packs its DNA into a surprisingly small volume.

But how is all this material organized so as to serve the infinitely complex requirements of a flatworm, bumblebee, shark, or human? Biologists have spent a good number of years trying to visualize the functional organization of chromosomes in the cell nucleus, and, while the task is far from finished, a lot of progress has been made.

Two important efforts to map the spatial arrangement of chromosomes were published in 2009 and 2014.[1] The researchers performed detailed analyses that yielded the schematic representations in the two figures below. The first of these studies showed that chromosomes are roughly organized into several functional compartments, represented by the different colors of the spherical globule in Figure 3.1. (The image depicts only the chromosomes, not the contents of the larger nucleus.) Any given chromosome simultaneously participates in multiple compartments, as indicated by the different colors of the linear (unfolded) chromosome shown at the top of the figure. You can, then, readily imagine the tortuous pathways of the intermingling chromosomes — the “twenty-four miles of string in a tennis ball” — constituting the overall globule.

The different compartments are distinguished by the kinds of genes residing in them and by the chromatin proteins, the modifications of those proteins, and the vast number of associated molecules in the nucleus that influence how those genes will be expressed and even what sort of products they will yield. In addition, researchers are widely agreed that the entire aggregate is more or less partitioned into two broader compartments, referred to as the “A” and “B” compartments. “A” tends to contain more active genes and to consist of more open chromatin, while “B” contains less active genes and more condensed chromatin.

Box 3.1

Some Standard Terminology

The usual formula has it that DNA makes RNA and RNA makes protein. The DNA double helix forms a kind of spiraling ladder, with pairs of nucleotide bases (“base pairs”) constituting the rungs of the ladder: a nucleotide base attached to one siderail of the ladder bonds with a base attached to the other siderail. These two bases, commonly referred to as “letters” of the DNA “text”, are normally complementary, so that, of the four different bases (abbreviated as A, T, C, and G), an A pairs only with a T (and vice versa), just as C and G are paired. Each siderail, with its attached nucleotide base, is considered a single *strand* of the double helix. Because the chemical subunits making up the siderails are asymmetrical and oriented oppositely on the two strands, the strands can be said to “point” in opposite directions.

The enzyme that *transcribes* DNA into RNA (thereby *expressing* a gene) must move along the length of the gene in the proper direction, separating the two strands and using one of them as a template for synthesizing a single-stranded RNA *transcript* — a transcript that complements the template DNA strand in much the same way that one DNA strand complements the other. It is by virtue of this complementation that the “code” for a protein is said to be passed from DNA to RNA. Once formed, the RNA may pass through the nuclear envelope to the cell’s cytoplasm, where it may be *translated* into protein.

It all makes for a neat, if extraordinarily simplistic story. For a fuller exploration of technical terms, see the glossary at https://bwo.life/mqual/glossary.htm.

Crucially, the image shown is a geometric idealization. It is designed to show certain principles of interweaving compartments, and is not meant to suggest that chromosomes are organized into a neat sphere. In reality, there is an almost infinitely complex and dynamic configuration involving not only internal relations among chromosomes, but also continual engagement with other contents and activities of the nucleus. Substantial portions of the “B” compartment reside near, and interact with, the outer envelope of the nucleus, whereas much of the “A” compartment lies more in the interior. During the processes of DNA replication and cell division (mitosis), the entire arrangement, for all its seemingly tangled complexity, “magically” transforms into a series of radically different configurations. (See, for example, Figure 3.3.)

The picture is always dynamic. Chromosomes *move*. Or, rather, they are brought into motion. Particular genes — which is to say, particular parts of chromosomes — can be shifted from one compartment to another, and the associations they form with other chromosomal

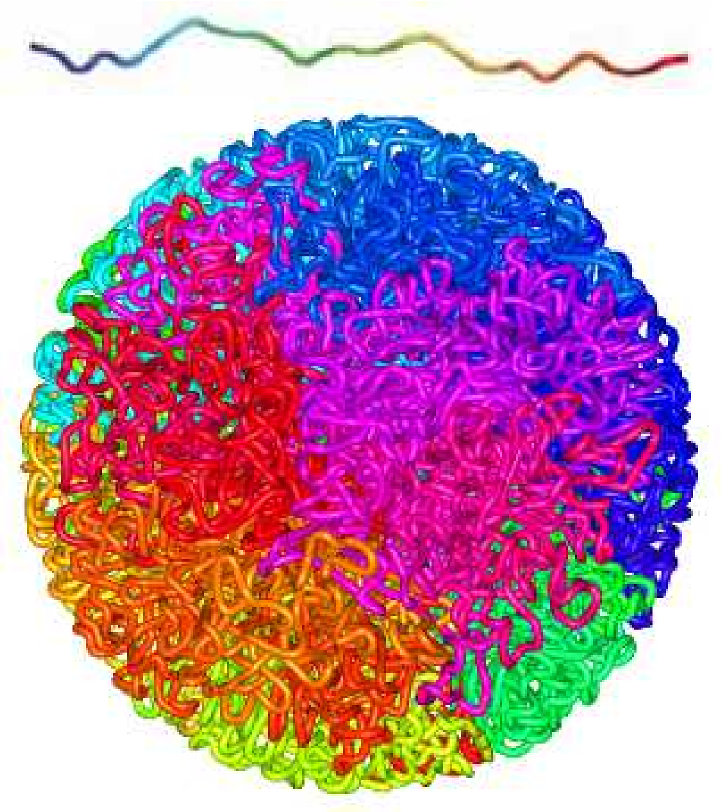

Figure 3.1. A schematic representation of a proposal for how human chromosomes are organized (at certain times) into a globular aggregate in the cell nucleus.[2]

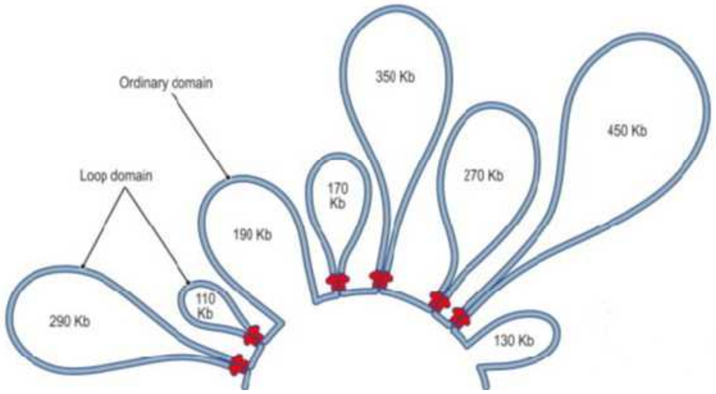

Figure 3.2. A schematic representation of DNA loops. “Kb” stands for “kilobases”, or thousands of “letters” of the “genetic code” — in this case, the number of letters strung out along the length of a chromosome loop. For example, the loop at far left is 290,000 letters long.[3] (On terminology, see Box 3.1.)

regions — whether on the same or different chromosomes — can be decisive for the regulation of gene expression. One way to picture a part of this dynamism is shown in Figure 3.2.

The figure illustrates a smaller-scale feature that would be impractical to include in Figure 3.1. The paired red marks at the point where a loop converges on itself indicate the presence of two copies of a particular protein, one of a number of molecules that play a role in loop formation. Note that the two loci where the protein binds a particular loop can be separated by thousands or hundreds of thousands of genetic “letters”.

(For comparison, while genes vary greatly in size, they average about 30,000 “letters” in length. And human chromosomes range from about 47 to 247 million “letters”.)

Of the two widely separated loci thus brought together, one may be near a gene while the other is near regulatory elements necessary for that gene to be expressed. Their coming together (or not) is therefore part of how genes come to be expressed (or not). And, likewise, the reconfiguration of such loops may be critical for the altered expression of genes as the cellular and organismal context changes.

But it’s not just the contact at the base of a loop that matters. Each loop as a whole forms its own domain, within which interactions typically occur more frequently than between more widely separated loci. And this organization of chromosomes into functional regions takes place at different scales, which have not at all been fully explored as yet. For example, researchers have identified “topologically associated domains” (TADs) dividing any given chromosome into regions of, say, one or two million “letters”. Interactions within such domains are more frequent than between domains. But there are no absolute rules in such matters. Sometimes the fraternizing bits of DNA are separated on their chromosome by tens of millions of “letters”, or reside on entirely different chromosomes.

We have so far hardly done more than hint at the true dynamism that enlivens our genetic heritage. The general picture of complex, three-dimensional organization has certainly galvanized molecular biologists. John Rinn, director of the Rinn Lab at Harvard, has said of the nuclear space and its chromosomal drama, “It’s genomic origami … It’s the shape that you fold [the genome] into that matters” (quoted in Zimmer 2015). According to the 2014 paper cited above, “A loop that turns a gene on in one cell type might disappear in another. A domain may move from subcompartment to subcompartment as its flavor changes. No two cell types [have their chromosomes] folded alike. Folding drives function.”[4] And Suhas Rao, the paper’s lead author and a researcher at Baylor College of Medicine’s Center for Genome Architecture, remarked:

> A loop is the fundamental fold in the cell’s toolbox. We found that the formation and dissolution of DNA loops inside the nucleus enables different cells to create an almost endless array of distinct three-dimensional folds and, in so doing, accomplish an extraordinary variety of functions (quoted in Physorg 2014).

Every overall configuration (involving many factors we have not yet considered) represents a unique balance between constrained and liberated expression of our total complement of 21,000 genes.[5] Moreover, new features of chromosome spatial and dynamic organization continue to be elucidated on a regular basis, and there appears to be no limit to the variety and scale of these features.

Think about all this dynamic form and movement for a while, and you may find yourself asking, along with me: What possible mechanism could ensure the *coherence* of all this movement and gesturing in relation to all the requirements of the trillions of cells in your or my body, or the tissues and organs into which those cells are organized, as we go about our endlessly varying activities under endlessly varying conditions?

Of dynamism and mystery in the cell nucleus

The chromosome, remarked Christophe Lavelle of France's Curie Institute, "is a plastic polymorphic dynamic elastic resilient flexible nucleoprotein complex."[6] There are many activities in which it participates, revealing significant form and organization. In order to visualize just one of these activities, consider a long, double-stranded rope whose two strands coil around each other, much like the two strands of a DNA molecule. If you twist a segment of this rope in a manner opposite to its natural spiraling, you will find that the strands tend to separate (that is, loosen, or become less tightly wound). And if you continue to twist, then the rope as a whole will begin to coil upon itself. Similarly, if you twist in the same direction as the rope's natural twist, you will tighten the winding of the strands, and if you continue twisting, the rope will again coil upon itself.

The DNA double helix can likewise be loosened by twisting, along with formation of coils, and it can also be tightened and coiled. In fact, it happens that both effects result wherever the enzymes transcribing DNA into RNA are at work. And this twisting in one direction or another in turn either encourages or discourages the expression of nearby genes.[7]

In other words, there are transient chromosome domains established by the twisting forces (torsion) that are communicated more or less freely (and not only by transcribing enzymes) along bounded segments of the chromosome. The loci within such a region share a common torsion, and this can attract a common set of regulatory proteins that read the changes as "suggestions" about activating or repressing nearby genes (Lavelle 2009; Kouzine et al. 2008). The torsion also tends to correlate with the level of compaction of the chromatin fiber, which in turn correlates with many other aspects of gene regulation.

Picture the situation concretely. Every bodily activity or condition presents its own requirements for gene expression. Whether you are running or sleeping, starving or feasting, rousing yourself to action or calming down, suffering a flesh wound or recovering from pneumonia — in all cases the body and many of its different cells have specific, almost incomprehensibly complex and changing requirements for differential expression of thousands of genes. And one thing (among countless others) bearing on this differential expression in all its fine detail is the coiling and uncoiling of chromosomes.

With so much concerted movement going on (including the looping we heard about earlier) how does the cell keep all those "twenty four miles of string in the tennis ball" from getting hopelessly tangled? We do at least know some of the players addressing the problem. For example, there are complex protein enzymes called *topoisomerases*, which the cell employs to help manage the spatial organization of chromosomes. Demonstrating a spatial insight and dexterity that might amaze those of us who have struggled to sort out tangled masses of thread, these enzymes manage to make just the right local cuts to the strands in order to relieve strain, allow necessary movement of individual genes or regions of the chromosome and prevent a hopeless mass of knots.

Some topoisomerases cut just one strand of the double helix, allow it to wind or unwind around the other strand, and then reconnect the severed ends. This alters the supercoiling of the DNA. Other topoisomerases can undo knots by cutting both strands, passing a loop of the chromosome through the gap thus created, and then sealing the gap again.

Imagine trying this with miles of string wrapped around millions of minuscule beads compacted into a few cubic inches of space, with the string all the while looping and squirming like a nest of snakes in order to bring all the right loci together so as to achieve the tasks of the moment. (And how are these tasks "known"?) I don't think anyone would claim to have the faintest idea how this is actually managed in a meaningful, overall, contextual sense, although great and fruitful efforts have been made to analyze the local forces and "mechanisms" at play in isolated reactions.

Does the lawfulness of molecular interactions explain global coherence?

We have scarcely begun to look at the dynamic aspects of the cell nucleus. Not only do chromosomes fold, loop, coil, and twist rather like a nest of snakes, but they engage in decisive and changing electrical interactions; they relocate from here to there within the nucleus, partly in order to associate with dynamically assembled collections of molecules important for regulating gene expression; and they are influenced by pushes and pulls from the fibers of the extra-nuclear cytoskeleton (Chapter 4).

Or again, DNA is said to "breathe" in rhythmical movements as it tightens and relaxes its embrace of the histone core particles mentioned earlier. And again, it breathes in a different sort of rhythm as the two strands of the double helix alternately separate and reunite at particular loci. And yet again, there are many profoundly significant structural novelties to which DNA lends itself, beyond the double helix. All this and much more is the cell's way of evoking the genetic performance that it needs — a performance that expresses the cell's own life and that of the organism as a whole.[8]

And so, when researchers refer to the "choreography" of the cell nucleus and the "dance" of chromosomes, as they sometimes do, their language is closer to being literal than many have imagined. If the organism is to survive, chromosomal movements must be well-shaped responses to sensitively discerned needs — all in harmony with innumerable dance partners, and all resulting in every gene being expressed or not according to the meaning of the larger drama. We can hardly help asking: If such choreography is how the organism lives and performs at the molecular level, what does this mean for the nature of molecular biological explanation?

Yes, the use of terms such as "dance" and "choreography" in molecular biology is rather distinctive. Some might call it eccentric. But this particular eccentricity has for some time now been creeping into the conventional technical literature. We have already heard of "genomic origami", an idea that has almost become a cliché. And we have also been told: "The statement, 'genomes exist in space and time in the cell nucleus' is a trivial one, but one that has long been ignored in our studies of gene function" — this according to two leaders of the current work: Job Dekker, head of a bioinformatics lab studying the spatial organization of genomes at the University of Massachusetts Medical School, and Tom Misteli, a research director at the National Cancer Institute. Recent investigations, they say, have taught us that "gene expression is not merely controlled by the information contained in the DNA sequence", but also by the "higher-order organization of chromosomes" and "long-range interactions in the context of nuclear architecture" (Dekker and Misteli 2015).

This last remark may startle some readers into the sudden realization that in all the foregoing there has been no discussion of the famed DNA *sequence* — the supposedly precise logical content of the "coded genetic program" that "makes us who we are". Why is that?

It looks very much as if the chromosome, along with everything else in the cell, is itself a manifestation of life, not a logic or mechanism explaining life. This performance cannot be captured with an abstract code. Gene regulation is defined less by static elements of logic than by the quality and force of its various gestures. Brought into movement by its surroundings, the chromosome becomes an expression of a larger context of living activity.

The fixation upon an abstract, neatly identifiable informational sequence has served well the compulsion among biologists to find precise, unambiguous, logically clean, and satisfyingly deterministic causal explanations. Nevertheless, what's been happening in rapidly intensifying fashion over the past couple of decades, has been a forced retreat from explanations of this sort. To cite a few key words and phrases from the contemporary literature: everything turns out to be mind-numbingly *complex*, which means, in part, that *context* makes all the difference. We are forced to try to understand how *regulatory networks*, intricate *feedback* loops, and the frequent *difficulty of distinguishing causes from effects* bear upon our biological understanding. Ultimately, we seem to be driven toward *systems biology*, an easily degraded term that many seem to prefer over the embarrassment (and richer meaning) of *holistic biology*.

What is not generally realized, however, is that this retreat *from* simplistic "causal mechanisms" suggests a movement *toward* a kind of explanation biologists have not yet come to terms with. It is, after all, one thing to explain, say, how a topoisomerase enzyme "mechanistically" passes one double-stranded section of DNA through another, and quite a different thing to ask how this activity — which *could* be carried out in countless different patterns — is made to harmonize with everything else going on at the molecular level in order to produce an overall, directed, coherent outcome for the cell as a whole. How might we make sense of the vast coordination of trillions of molecular events in the interest of a larger picture that is subject to continual change, as when a cell initiates the transition leading toward cell division?

The globular and peculiarly organized aggregation of chromosomes we saw in Figure 3.1 is a long way, for example, from the the chromosomal organization during DNA replication, and likewise from the striking configurations we observe with the mitotic spindle during cell mitosis (Figure 3.3). What is a topoisomerase to do when it is in contact with a particular locus of a DNA molecule — a particular locale among the intricately folded, 6.4 billion nucleotide bases ("letters") of a human cell? How does it connect with the larger drama, so as to play its local role properly? Or is it rather that the larger drama connects with the individual topoisomerase?

James Wang, the Harvard University molecular biologist who discovered the first topoisomerase, seems to have had some awareness of the problem. Writing about the striking capability of a topisomerase to untie a DNA knot by cutting through the double helix and later putting it back together again — all without disturbing the critical continuity of the original chemical structure — he expresses his wonder:

> When we think a bit more about it, such a feat is absolutely amazing. An enzyme molecule, like a very nearsighted person, can sense only a small region of the much larger DNA to which it is bound, surely not an entire DNA [molecule]. How can the enzyme manage to make the correct moves, such as to untie a knot rather than make the knot even more tangled? How could a nearsighted enzyme sense whether a particular move is desirable or undesirable for the final outcome? (Wang 2009)

Wang presumably knows that a molecule does not *sense* anything at all. And he surely also knows that the topoisomerase always has an adequate physical basis for doing what it does in the place where it is. And yet this physically lawful activity (which is what Wang concerns himself with) does not yet get us to an understanding of the radically different

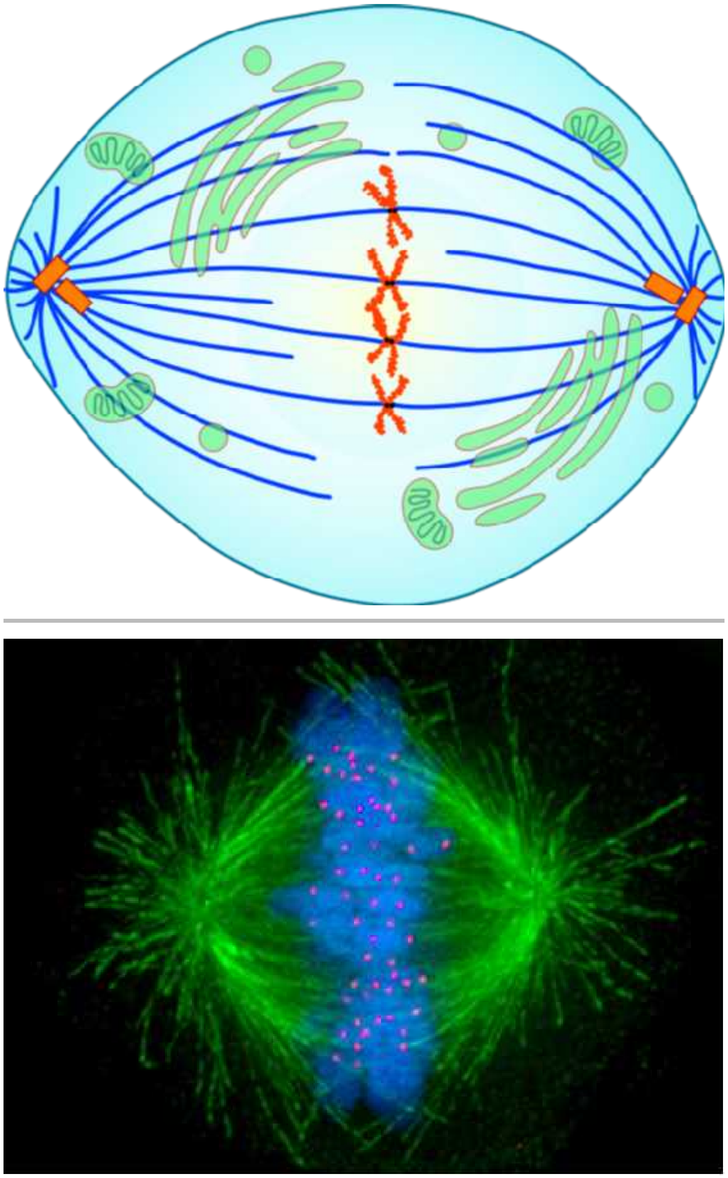

Figure 3.3. (*top*:) A schematic representation of a mitotic spindle in a cell with just four duplicated chromosomes. (*bottom*:) An artificially colored image of the mitotic spindle in a human cell, showing microtubules in green, chromosomes (DNA) in blue, and kinetochores in red. A kinetochore is a protein structure that temporarily holds a chromosome and its duplicate together while also providing an anchor for a "thread" of the mitotic spindle. In the following phase of mitosis, each chromosome and its duplicate will be pulled apart, destined for different daughter nuclei.[9]

activities and outcomes at the cellular level. It doesn't help to explain the different patterns we see, for example, as a cell proceeds through the many distinctive phases of cell division.

Yes, we have every reason to believe that whatever happens, happens lawfully. But this still leaves us with the question, "How does our understanding of the overall coherence of cellular and organismal processes relate to the lawfulness we unfailingly observe whenever we isolate particular interactions and analyze them in physical and chemical terms?" That lawfulness continues the same throughout all cellular activity of the most diverse sorts, and it does not seem to have any obvious provisions for explaining the unique, ever-varying principles of coordination and coherence governing biological entities ranging from cells to organs to the entire range of whole organisms.

Where are we now?

Yes, the Cell's Genomic Performance Is Complex!

Not only is all the regulatory activity and the resulting, three-dimensional "dance" of our genome exceedingly complex, it also shows us clearly that we are really looking at a whole-cell and whole-organism performance. The genome can do nothing of itself, and what the organism does with it comes from every possible direction and also continually varies in time with ever-changing conditions. We will learn more about this complexity in further chapters, especially Chapters 7 and 14. The question how everything is coordinated in a useful, need-fulfilling, and meaningful way seems to stymie every effort at conventional scientific explanation.

Indeed, you will have noticed in these first chapters that we seem to be raising a lot of questions! You can count on one thing — the question-raising will never come to an end. This is, in the first place, what all good science should do — raise decisive questions with ever greater clarity. But we can also nourish a hope that is not common in today's science: namely, that by continuing to describe the life of organisms in a revelatory way — acknowledging the narrative and holistic character of beings whose lives manifest from the immaterial "inner" toward the material "outer" — we will find the description itself coming more and more to constitute exactly the sort of *biological* understanding and explanation we can best look for. We will explicitly address this sort of understanding, and how it connects to our ideas of causality, in Chapter 12 ("Is a Qualitative Biology Possible?").

We will also confront — especially in Chapters 13 and 24 — how our questions relate to the problem of the thought-full character of the material world generally. And while just about the whole book raises a question about the relation between isolated and specific living processes, on one hand, and their larger context, on the other, we will try to make this question more pointed in Chapter 8 ("The Mystery of an Unexpected Coherence"). And we will, finally, need to address here and there the misdirected charge of "vitalism" that some of this discussion seems inevitably to provoke.

Notes

1. See Lieberman-Aiden 2009 and Rao 2014.

2. Figure 3.1 credit: Miriam Huntley, Rob Scharein, and Erez Lieberman-Aiden. Linear chromosome at top of figure: Ed Yong (CC BY-SA 3.0).

3. Figure 3.2 credit: from Rao et al. 2014.

4. The quote comes from the author's video abstract of their paper in *Cell*. See Rao 2014.

5. Toward the end of the Human Genome Project in 2000, according to a report in *Nature*, "geneticists were running a sweepstake on how many genes humans have, and wagers ranged from tens of thousands to hundreds of thousands. Almost two decades later, scientists armed with real data still can't agree on the number". Current estimates tend to run between 19,000 and 22,000, but recent criticisms "underscore just how difficult it is to identify new genes, or even to define what a gene is" (Willyard 2018).

6. Lavelle 2009. Nucleoproteins are proteins bound up with DNA or RNA.

7. To get more specific about it, think of it this way. If, taking a double-stranded rope in hand, you insert a pencil between the strands and force it in one direction along the rope, you will find the strands winding ever more tightly ahead of the pencil's motion and unwinding behind. An RNA polymerase, which must separate the two strands of DNA as it transcribes a gene, can in the right circumstances have an effect rather like the pencil: it will cause what is called "negative supercoiling" (loosening of the double helix spiral) behind itself, and "positive supercoiling" ahead. And if, say, negative supercoiling has already occurred in the region being transcribed, the polymerase will find it much easier to separate the two strands and do its work. So in this way the variations in coiling along the length of a chromosome either encourage or discourage the transcription of particular genes.

8. To get a rough sense merely for the number of significant variations in DNA double helix conformation and the kind of effect they can have, here is a statement enumerating such variations and their bearing on a single regulatory feature, namely, the position of certain nucleosomes (which themselves play a key role in regulation of gene expression). There is no need to understand the different technical terms in order to get a feel for the complexity of the sculptural details of any particular stretch of DNA, and the kind of role these details can play in relation to gene expression.

> Variant –1 nucleosomes exhibited a preference for sequences with altered features such as propeller twist, opening, electrostatic potential, minor groove width, rise, stagger, helix twist, and shear and roll. Variant –1 nucleosomes that shifted downstream in KDM5B-depleted ES cells preferred sequences with increased propeller twist, opening, electrostatic potential, stagger, minor groove width, rise, and buckle, while –1 variant nucleosomes that shifted upstream preferred sequences with decreased propeller twist, opening, electrostatic potential, stagger, minor groove width, rise, and buckle … Combined, these findings suggest that DNA shape predicts sequence preferences of canonical nucleosomes and variant nucleosomes. These results also suggest that histone DNA binding patterns such as

bending or electrostatic interactions may be influenced by posttranslational modifications such as H3K4 methylation (Kurup, Campeanu and Kidder 2019).

9. Figure 3.3 credit: Both images are in the public domain via the Creative Commons.

Sources

Dekker, Job and Tom Misteli (2015). “Long-Range Chromatin Interactions”, *Cold Spring Harbor Perspectives in Biology* 2015;7:a019356. doi:10.1101/cshperspect.a019356

Kouzine, Fedor, Suzanne Sanford, Zichrini Elisha-Feil, et al. (2008). “The Functional Response of Upstream DNA to Dynamic Supercoiling *in Vivo*”, *Nature Structural and Molecular Biology* vol. 15, no. 2 (February), pp. 146-54. doi:10.1038/nsmb.1372

Kurup, Jiji T., Ion J. Campeanu and Benjamin L. Kidder (2019). “Contribution of H3K4 Demethylase KDM5B to Nucleosome Organization in Embryonic Stem Cells Revealed by Micrococcal Nuclease Sequencing”, *Epigenetics & Chromatin* vol. 12, no. 20. doi:10.1186/s13072-019-0266-9

Lavelle, Christophe (2009). “Forces and Torques in the Nucleus: Chromatin under Mechanical Constraints”, *Biochemistry and Cell Biology* vol. 87, pp. 307-22. doi:10.1139/O08-123

Lieberman-Aiden, Erez, Nynke L. van Berkum, Louise Williams et al. (2009). “Comprehensive Mapping of Long-Range Interactions Reveals Folding Principles of the Human Genome”, *Science* vol. 326 (October 9), pp. 289-93. doi:10.1126/science.1181369

Lewontin, R. C. (1992). “The Dream of the Human Genome”, *New York Review* (May 28), pp. 31-40. https://www.nybooks.com/articles/1992/05/28/the-dream-of-the-human-genome/

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

Moss, Lenny (2012). “Is the Philosophy of Mechanism Philosophy Enough?” *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* vol. 43, no. 1 (March), pp. 164-72. doi:10.1016/j.shpsc.2011.05.015

Physorg (2014a). “Scientists Map the Human Loop-ome, Revealing a New Form of Genetic Regulation” (December 11). https://phys.org/news/2014-12-scientists-human-loop-ome-revealing-genetic.html

Rao, Suhas S. P., Miriam H. Huntley, Neva C. Durand et al. (2014). “A 3D Map of the Human Genome at Kilobase Resolution Reveals Principles of Chromatin Looping”, *Cell* vol. 159, pp. 1665-80 (December 18). doi:10.1016/j.cell.2014.11.021

Talbott, Stephen L. (2010). “The Unbearable Wholeness of Beings”, *The New Atlantis* no. 29 (fall), pp. 27-51. Available at https://thenewatlantis.com/publications/the-unbearable-wholeness-of-beings. Original version published in *NetFuture* no. 29 (fall), pp. 27-51. Also available at https://BiologyWorthyofLife.org/mqual/genome_5.htm.

Wang, James C. (2009). *Untangling the Double Helix*. Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press.

Willyard, Cassandra (2018). “New Human Gene Tally Reignites Debate”, *Nature* vol. 558 (June 21), pp. 354-55. doi:10.1038/d41586-018-05462-w

Zimmer, Carl (2015). “Is Most of Our DNA Garbage?” *New York Times* (March 5). https://www.nytimes.com/2015/03/08/magazine/is-most-of-our-dna-garbage.html

CHAPTER 4

The Sensitive, Dynamic Cell

Throughout a good part of the twentieth century, cell biologists battled over the question, “Which exerts greater control over the life of the cell — the cell nucleus or the cytoplasm?” (Sapp 1987). From mid-century onward, however, the badge of imperial authority was, by enthusiastic consensus, awarded to the nucleus, and especially to the genes and DNA within it. “Genes make proteins, and proteins make us” — this has been the governing motto, despite both halves of the statement being false (which will become ever clearer as we proceed).

The question for our own day is, “Why would anyone think — as the majority of biologists still do — that any part of a cell must possess executive *control* over all the other parts?” We have already caught our first glimpse of the performances in the nucleus (see Chapter 3), and these hardly testify to domination by a single, controlling agent. Now we will broaden our outlook by making a first approach to the rest of the cell — the cytoplasm, along with its organelles and enclosing membrane.

It would be well to remind ourselves before we proceed, however, that, whatever else it may be, an organism is a physical being. Its doings are always in one way or another *physical* doings. This may seem a strange point to need emphasizing at a time when science is wedded to materialism. And yet, for the better part of the past century problems relating to the material coordination of biological activity were largely ignored while biologists stared, transfixed, into the cell nucleus. If they concentrated hard enough, they could begin to hear the siren call of a dematerialized, one-dimensional, informational view of life.

The idea of a genetic *code* and *program* proved compelling, even though the program was never found and the supposedly fixed code was continually rewritten by the cell in every phase of its activity. So long as one lay under the spell woven by notions of causally effective information and code, problems of material causation somehow disappeared from view, or seemed unimportant. And so, freed from “mere” material constraint, programmatic Information became rather like the Designer of the intelligent design advocates.

Surely, even if they are not the decisive causes usually imagined, genes do connect in *some* manner with the features they were thought one-sidedly to explain. But this just as surely means they must connect physically and meaningfully, via movements and transformations of substance testifying to an underlying narrative (Chapter 2) — not merely logically, through the genetic encoding of an imagined program. And what we saw in Chapter 3 about the significant movements and gesturings of chromosomes is only the beginning of the story.

Does the cell possess its own "senses" and "limbs"?

Let's continue by taking note of the cytoskeleton (Figure 4.1), which plays a key role in the cell's physical movement. It consists of many exceedingly thin molecular filaments and tubules, visible only under powerful microscopes. Many of these are growing at one end and perhaps shrinking at the other end, or else disassembling altogether even as new filaments are establishing themselves. Through this dynamic activity — this constant growth and dissolution of minuscule fibers — the cell gains its more or less stable shape and organization.

Cellular organelles, to which the cytoskeleton attaches, are positioned and re-positioned as the cytoskeleton somehow "senses" internal needs, while also responding to external stresses such as stretching or compression. Beyond that, the filaments and tubules, by dynamically managing the distribution of forces within the cell as a whole, help to enable and guide its movements so that it can find its proper place among the millions of cells in its immediate environment.

And the cells of our bodies do move. Literal rivers of cells shape the young embryo. So, too, migrating cells in and around a wound cooperate in restoring the damaged architecture. In every tiniest hair follicle niche, as well as throughout our tissues generally, cells move, replace dying neighbors, and reorganize themselves. And even while remaining in one place, cells must continually adapt their form to their immediate environment — certainly a major task in the rapidly growing embryo and fetus. But the stresses and tensions of that environment are in turn the partial result of interconnected cytoskeletal activities in all the cells of the local tissue.

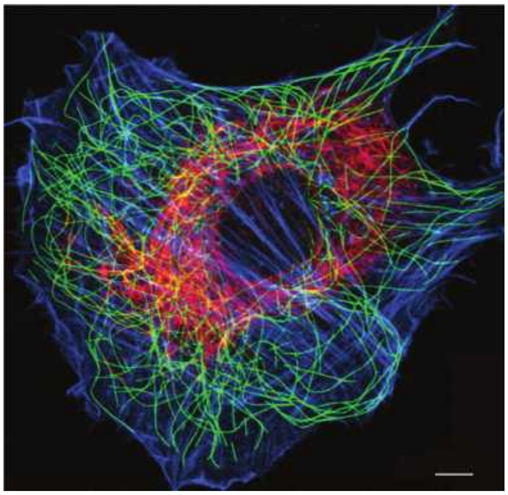

Figure 4.1. A cultured fibroblast cell, specially prepared so as to show features of the cytoskeleton in artificial color: narrow actin filaments (blue); wider microtubules (green); and intermediate filaments (red). The dark and roughly circular (spherical) region near the center is the cell nucleus.[1]

The cytoskeleton not only supports cell migration, but also provides pathways for the orchestrated movement of substances within the cell. A protein molecule is not of much use if it cannot find its way to where it is required. Individual molecules and protein complexes are shifted about along these cytoskeletal pathways, as are the voluminous contents of large-capacity, membrane-bound, transport structures ("vesicles"). These latter can "bud off" from various internal membranes of the cell and then move, along with their cytoplasmic contents, to a particular destination where, having released their contents, they are degraded and recycled.

Such directed movements are essential to the life of the cell. Where an enzyme or signaling molecule goes in a cell is decisive for its function. Some molecules, for example, are outward-bound to, and through, the cell surface on signaling missions to distant reaches of the body. Meanwhile, others are inward-bound on different signaling missions. (Hormones, secreted by cells of a gland at the start of their journey, and then received by cells in various other parts of the body, illustrate both sorts of movement.) Some molecules produced in a cell are destined for a particular locus on the highly differentiated cell membrane, while others are targeted to any of a virtually infinite number of possible stopping places somewhere in the cell's "intricate landscape of tubes, sacs, clumps, strands and capsules that may be involved in everything from intercellular communication to metabolic efficiency."[2]

But the cytoskeleton is not just a cytoskeleton. The filaments and tubules themselves are teeming with associated regulatory molecules. As of a decade ago more than 150 proteins capable of binding to just one type of filament — actin — had already been identified. As one researcher has put it: "Despite the connotations of the word 'skeleton', the cytoskeleton 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" (Fletcher 2010).

There is scarcely any aspect of cellular functioning in which the cytoskeleton fails to play a role. On the exterior side, it connects with the cell's outer ("plasma") membrane, where it helps to import substances from the environment while also facilitating the adhesion of extracellular molecules and other cells. Through its interaction with the extracellular matrix, it contributes to the mechanical stiffness and coherence of entire tissues. On the interior side, it engages with the nuclear membrane and the specialized filaments underlying that membrane. These filaments are vital regulators of gene expression. In this way the cytoskeleton links various sorts of extracellular signals, both mechanical and biochemical, to the nucleus and its chromosomes, providing a foundation for holistic behavior involving much more than the individual cell.

There are many ways to affect gene expression, and they do not all occur in the cell nucleus. For example, a key part of this expression is the translation of RNA molecules into proteins, which occurs in the cytoplasm. Evidence suggests that "the physical link between cytoskeletal and translational components helps dictate both global and local protein synthesis". But (as is all too typical) the causal effects work both ways: "specific translation factors are able to affect the organization of cytoskeletal fibres".[3]

The cytoskeleton plays many other roles, not least by ensuring the proper separation of mitotic chromosomes, the division of a cell into two daughter cells, and the correct allocation of chromosomes to those daughter cells. (See Figure 3.3, where the mitotic spindle, shown in green, consists of cytoskeletal fibers.) It is perhaps unsurprising, then, that some have seen the cytoskeleton, with its nuanced organizational "skills", as the seat of cellular intelligence or the "brain" of the cell. However, we need not invite a misleading anthropomorphism in order to acknowledge the subtle and nuanced organizational activity — the *narratively intelligible* activity (Chapter 2) — realized through the dynamics of cytoskeletal movement.

One thing is certain: neither the cytoskeleton's moment-by-moment dynamics nor the coherent and intelligible aspect of its activity can be ascribed to "instructions" from genes — or even to the physical laws bearing on cytoskeletal proteins. As the matter was summarized by Franklin Harold, an emeritus professor of biochemistry and molecular biology at Colorado State University, “One cannot predict the form or function of these complex [cytoskeletal] ensembles from the characteristics of their component proteins”. And yet, Harold went on, “When seen in the context of the parent cell the arrangement of the molecules becomes quite comprehensible”. He then raised the obvious question: “How is the cytoskeleton itself so fashioned that its operations accord with the cell’s overall ‘plan’ and generate its particular morphology time after time?”[4]

Harold answered the question merely by expressing confidence that understanding will eventually come. And surely it will. But we can be equally sure that it will not come before we have penetrated more deeply the problem: How does a living context, or whole — in this case, the cell with its “overall plan” — manage to express itself through all its parts?

In an integral, organic whole, we can assume the “viewpoint” of many parts in such a way as to make each one *momentarily* seem to be the coordinating “master” element. This is why the cytoskeleton, just as much as our genes, might appear to explain everything that goes on. With wonderful sensitivity it “feels out” the surfaces of the cell and all its organelles. The balance of forces maintained by the fibers shapes the cell, dynamically positions the organelles, and both guides and helps to power the critical movement of the cell within its environment. As we have seen, the cytoskeleton likewise plays a key role in moving substances to their functional locations within the cell. And it is a decisively important regulator of gene activity.

And yet, this does not make the cytoskeleton a master regulator. The truth is simply that, to one degree or another, each part of an organic whole bears that whole within itself — is informed by, and expresses, the whole. The idea of a master regulator arises only when we insist on viewing a specific part in isolation from the whole so as to identify single, local, and unambiguous causal interactions. We then say that this part *makes* certain things happen. The fact that the part is itself made to happen by the very things it supposedly accounts for then tends to be ignored. We lose sight of the fluidity and physical indeterminism of the living context — an indeterminism whose meaning and coherence become visible only when we allow particular physical causes to “disappear” into the unifying *narratives*, or stories, of the organism’s life (Chapter 2). In much the same way, we experience physical sounds and gestures disappearing into the meaning of the speech we hear.

The sensitive "skin" and organelles of the cell

Interestingly, the cell membrane ("plasma membrane") is likewise a highly dynamic feature that has been seen as a decisive coordinator of cellular activity, and even as a seat of cellular intelligence. It is here that we see "decisions" continually being made about which substances and signals — from among the endlessly streaming crowds passing through the neighborhood — are to be admitted into the cell and which ones are "foreign", or else unnecessary at the moment. Here, perhaps more than anywhere else, is where cellular identity is established and "self" is distinguished from "other". This happens partly by means of protein receptors ("sensors") embedded in, or attached to, the lipid matrix of the membrane.

Here, too, everything flows (which is one reason why any image like the two below is a kind of frozen lie, despite being useful when approached with the right awareness). Molecules continually associate with, and dissociate from, the membrane, even as they undergo various modifications that redirect their functioning. They also migrate within the membrane, forming specialized communities that are in no two locales exactly the same. All the while portions of the membrane, along with cytoplasmic contents, are "pinched off" as more or less spherical vesicles that, once they are fully detached, move elsewhere, either externally to the cell or internally. At the same time, selected vesicles from external sources fuse with the membrane and release their contents into the cell's interior.

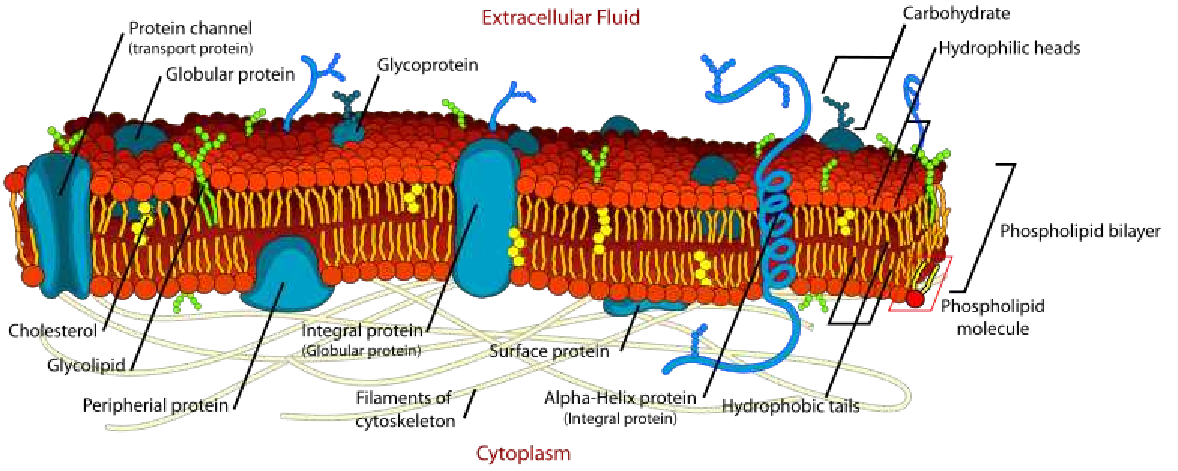

Figure 4.2. See main text.[5]

Much the same is true of all the interior membranes delimiting the various organelles of the cell (Figure 4.3). These, too, "harbor sensitive surveillance systems to establish, sense, and maintain characteristic physicochemical properties that ultimately define organelle identity. They … play active roles in cellular signaling, protein sorting, and the formation of vesicular carriers."[7]

Membranes, then, not only structure the cell into distinctive compartments and organelles, but they also "oversee" the characteristic and essential contents of those compartments and play decisive roles in managing the ceaseless and massive intercommunication among them.

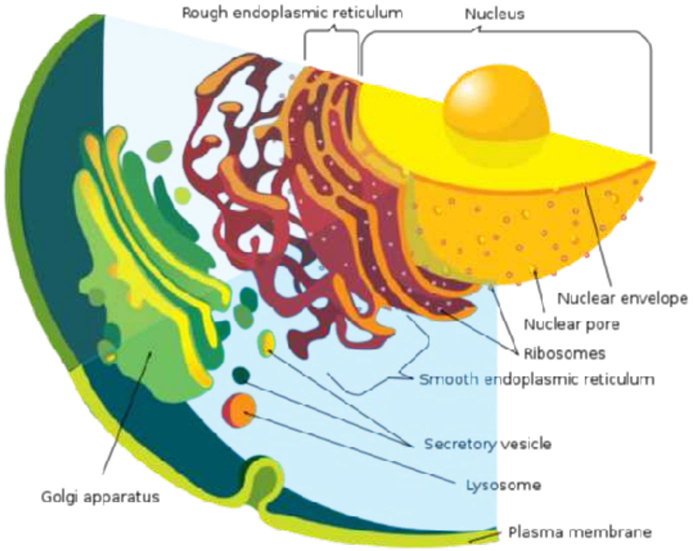

Figure 4.3. Schematic representation of the internal membrane systems of a nucleated cell.[6]

All this finely discriminating activity is going on, as the eminent cell biologist, Paul Weiss, wrote in 1973, while "the cell interior is heaving and churning all the time" (Weiss 1973, p. 40). Everything is watery movement of substances and transformation of organizational structure, and yet the cell's identity and unified character are maintained. Movement itself is what expresses the character and life of the cell and the organism. The intricately choreographed flows and chemical transactions in plasm and membrane are responsive to the ever-unpredictable conditions of the moment, and are the means by which the cell not only stays true to itself, but also remains in harmony with its larger environment.

The dynamics of this material accomplishment are a long way from the clean, informational logic commonly associated with genes. Lenny Moss, a molecular biologist who transformed himself into one of our most insightful philosophers of biology, had this to say about the relation between cellular membranes and genes:

> The membranous system of the cell, the backbone of cellular compartmentalization, is the necessary presupposition of its own renewal and replication. 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 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.[8]

From information to life

Returning for a moment to our introductory question about the control of the cell by its genes: perhaps we have now gained our first feeling for how the cell and organism as a whole can flexibly and contextually express itself through any one of its parts, including its DNA and chromosomes — a fact we will get much more specific about in the Technical Supplement, as well as in Chapter 7. If we think of the genome as an almost infinitely complex informational structure, there is no reason not to think, for example, of the cytoskeleton and membranes of a cell as at least equal bearers of vital information. However, it is also important to recognize the illegitimate aspects of this comparison.

In particular, the concept of information as normally applied to DNA is a quantitative one. It depends on the existence of discrete, iterated elements (“letters” of the “code”), any one of which can take on certain precise values. But everything we know about the “heaving and churning” interior of the cell — including even the coiling and looping of chromosomes we saw in Chapter 3 — tells us that we are looking at boundless and continuous variations of form and gesture whose depth of meaning is both non-quantifiable and vastly more profound than any quantifiable features we can abstract from it.

To ask about the amount of information in various aspects of the cellular performance (including the performance of chromosomes) is rather like asking about the amount of information in Stravinsky’s ballet, “The Rite of Spring”. It would be one thing to define informational quantities in terms of some more or less arbitrary method of choreographic notation (“code”), and quite another to consider the expressive content of the ballet itself.

So, too, our means for quantifying the informational content of a genomic sequence bears little relation to the material gestures expressing the cell’s life. The truth here will become even more vivid when we look (in Chapter 6) at the context-dependence that biologists freely acknowledge at every turn.

WHERE ARE WE NOW?

The cell is reflected in its parts

In this chapter (as will happen throughout much of the book) we have had thrown at us the question of the relation between part and whole. The cytoskeleton participates in and seems to represent the whole cell to such a degree that some are inclined to see it — and not the genetic material — as the “controlling” element of the cell. But neither point of view is satisfactory. We are continually forced back to nothing less than the whole itself, not as a mechanistically controlling entity, but rather as the narrator of the ongoing drama that is the organism’s life.

We will hear more about the cytoskeleton, for example in Chapter 5 and Chapter 21. The main lesson for the moment is that the cell is a material whole in its own right. In a multicellular organism it is, of course, a *relative* whole. But the fact is — as we will take specific note of in Chapter 6 — *every* organism is a relative whole: it is not only reflected in its parts, but it is itself caught up in, and is a reflection of, its encompassing community and environment.

We have seen that if the cytoskeleton is an expression of the whole cell, so, too — even if in very different ways — are the various cellular membranes. By noting the complementary manner in which these two complex features work together to express a cell’s living character, we can get a feeling for the integral unity of a biological whole. Perhaps (although I do not discuss this here) the linear character of the cytoskeletal filaments and the more globular, enclosing character of the membranes tell us something about the polarity out of which the living unity of the cell arises.[9]

Notes

1. Figure 4.1 credit: courtesy of Harald Herrmann, University of Heidelberg, Germany.

2. Kwok 2011. Here is a further description (from Plankar et al. 2012) of the various roles of the cytoskeleton:

> The cytoskeleton, in addition to its classical structural-mechanical role, integrates many signalling pathways, influences the gene expression, coordinates membrane receptors and ionic flows, and localizes many cytosolic enzymes and signalling molecules, while at the same time it represents an immense, electrically active catalytic surface for metabolic interactions. Together with cell adhesion molecules and the extracellular matrix, it forms a tensionally integrated system throughout the tissues and organs, which is able to coordinate gene expression via mechano-transduction. Given the strong relationship between mechanical and electromagnetic excitations in the microtubules (piezoelectricity) and their well-established organising potential, a weakened EM field may thus influence both cell and tissue aspects of carcinogenesis.

3. Kim and Coulombe 2010. The use of words such as “dictate” to suggest unambiguous causation is extremely common in all the literature of molecular biology. And almost as common is the immediate contradiction of this language, as we see here. For more on this, see Chapter 9.

4. Harold 2001, p. 125. Harold makes his question more emphatic with a little elaboration:

> How, for instance, do [the cell’s] famously fluid membranes hold their shape? How does the endomembrane system as a whole acquire its spatial orientation and location, while the cell of which it is a part grows, divides and moves around? ... In a nutshell, the cytoskeleton is responsible for the mechanical intergration of cellular space; unpacked, this phrase covers a host of actions and interactions, mediated by a large and growing ensemble of proteins. ... [Moreover, the cytoskeleton itself] is subject to frequent remodelling. Mitosis, for instance, entails the dissolution of much of the cytoskeleton; its components are redeployed in the service of cell division, and subsequently reconstituted in their former order. Everything is in flux, but in a regulated purposeful manner (pp. 123-24).

5. Figure 4.2 credit: Mariana Ruiz, edited by Alokprasad84 (CC BY-SA 3.0).

6. Figure 4.3 credit: Mariana Ruiz Villareal (CC BY-SA 3.0).

7. Radanović, Reinhard, Ballweg et al. 2018. Emphasis added.

8. Moss 2003, p. 95. Pages 76-98 in Moss’ book provide an excellent overview of the dynamics associated with cellular membranes.

9. One thing these opposing qualitative characters remind me of is a rather bold saying by Samuel Taylor Coleridge at the beginning of the famous Chapter XIII of *Biographia Literaria*:

> Grant me a nature having two contrary forces, the one of which tends to expand infinitely, while the other strives to apprehend or *find* itself in this infinity, and I will cause the world of intelligences with the whole system of their representations to rise up before you (Coleridge 1906).

And this in turn might remind us of a remark by Jakob Boehme:

> Nothing without contrariety can become manifest to itself; for it has nothing to resist it, it goes continually of itself outwards, and returns not again into itself (quoted in McFarland 1981).

That sounds rather like a picture of a cell with growing cytoskeletal fibers, but no enclosing membranes.

Sources

Coleridge, Samuel Taylor (1906). *Biographia Literaria*. London: J. M. Dent & Sons. Originally published in 1817.

Fletcher, Daniel A. and R. Dyche Mullins (2010). “Cell Mechanics and the Cytoskeleton”, *Nature* vol. 463 (January 28), pp. 485-92. doi:10.1038/nature08908

Harold, Franklin M. (2001). *The Way of the Cell: Molecules, Organisms and the Order of Life*. Oxford: Oxford University Press.

Kim, Seyun and Pierre A. Coulombe (2010). “Emerging Role for the Cytoskeleton as an Organizer and Regulator of Translation”, *Nature Reviews Molecular Cell Biology* vol. 11 (January), pp. 75-81. doi:10.1038/nrm2818

Kwok, Roberta (2011). “The New Cell Anatomy”, *Nature* vol. 480 (December 1), pp. 26-28. doi:10.1038/480026a

McFarland, Thomas (1981). *Romanticism and the Forms of Ruin: Wordsworth, Coleridge, and Modalities of Fragmentation*. Princeton NJ: Princeton University Press.

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

Moujaber, O. and U. Stochaj (2019). “The Cytoskeleton as Regulator of Cell Signaling Pathways”, *Trends in Biochemical Sciences*. https://doi.org/10.1016/j.tibs.2019.11.003

Plankar, M., E. Del Giudice, A. Tedeschi, and I. Jerman (2012). “The Role of Coherence in a Systems View of Cancer Development”, *Theoretical Biology Forum* vol. 105, no. 2 (January 1), pp. 15-46.

Radanović, Toni, John Reinhard, Stephanie Ballweg et al. (2018). “An Emerging Group of Membrane Property Sensors Controls the Physical State of Organellar Membranes to Maintain Their Identity”, *Bioessays*. doi:10.1002/bies.201700250

Sapp, Jan (1987). *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics*. Oxford: Oxford University Press.

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

Chapter 5

Our Bodies Are Formed Streams

In this materialist era, we like our reality *hard* and our truths *weighty* and *rock solid*. We may accept that there are states of matter less substantial than rocks, but in our imaginations we turn even fluids and gases into collections of tiny *particles* more or less closely bound together. Similarly, in our reconstructions of physiological processes, *material structures* come first, and only then can movement, flow, and meaningful activity somehow occur.

How, after all, can there be movement without *things* to do the moving? (It's easy to forget that energy, fields, and forces are not things!) Ask someone to describe the circulatory system, and you will very likely hear a great deal about the heart, arteries, veins, capillaries, red blood cells, and all the rest, but little or nothing about the endless subtleties of circulatory *movement* through which, for example, the structured heart first comes into being.[1]

Yet there is no escaping the fact that we begin our lives in a thoroughly fluid and plastic condition. Only with time do relatively solid and enduring structures precipitate out as tentatively formed "islands" within the streaming rivers of cells that shape the life of the early embryo. As adults, we are still about seventy percent water.

One might think quite differently based on the scientific rhetoric to which we are daily exposed. This could easily lead us to believe that the real essence and solid foundation of our lives was from the beginning rigidly established inside those very first cells. There we find DNA macromolecules that, in a ceaseless flood of images, are presented to us as crystalline forms in the shape of a spiraling ladder — a ladder whose countless rungs constitute the fateful stairway of our lives. So, too, with the proteins and protein complexes of our bodies: we have been told for decades that they fold precisely into wondrously efficient *molecular machines* whose all-important functions are predestined by the DNA sequence.

The trouble is, biological researches of the last few decades have not merely hinted at an altogether different story; they have (albeit sometimes to deaf ears) been trumpeting it aloud as a theme with a thousand variations. Even the supposedly "solid" structures and molecular complexes in our cells — including the ones we have imagined as strict determinants of our lives — are caught up in functionally significant movement that the structures themselves can hardly have originated. (See Chapter 3 and Chapter 4.)

Nowhere are we looking either at a static sculpture or at controlling molecules responsible for the sculpting. In an article in *Nature* following the completion of the Human Genome Project, Helen Pearson (2003) interviewed many geneticists in order to assemble the emerging picture of DNA. One research group, she reported, has shown that the molecule is made "to gyrate like a demonic dancer". Others point out how chromosomes "form fleeting liaisons with proteins, jiggle around impatiently and shoot out exploratory arms". Phrases such as "endless acrobatics", "subcellular waltz", and DNA that "twirls in time and space" are strewn through the article. "The word 'static' is disappearing from our vocabulary", remarks cell biologist and geneticist Tom Misteli, a Distinguished Investigator at the National Cancer Institute in Bethesda, Maryland.

Everywhere we look, shifting form and movement show themselves to be the “substance” of biological activity. The physiological narratives of our lives play out in gestural dramas that explain the origin and significance of structures rather than being explained by those structures.

Hannah Landecker, a professor of both genetics and sociology at UCLA, having looked at the impact of recent, highly sophisticated cellular imaging techniques on our understanding, has written: “The depicted cell seems a kind of endlessly dynamic molecular sea, where even those ‘structures’ elaborated by a century of biochemical analysis are constantly being broken down and resynthesized.” And she adds: “It is not so much that the structures begin to move, but movements — for example in the assembly and self-organization of the cytoskeleton — begin to constitute structure” (Landecker 2012). See Figure 5.1.

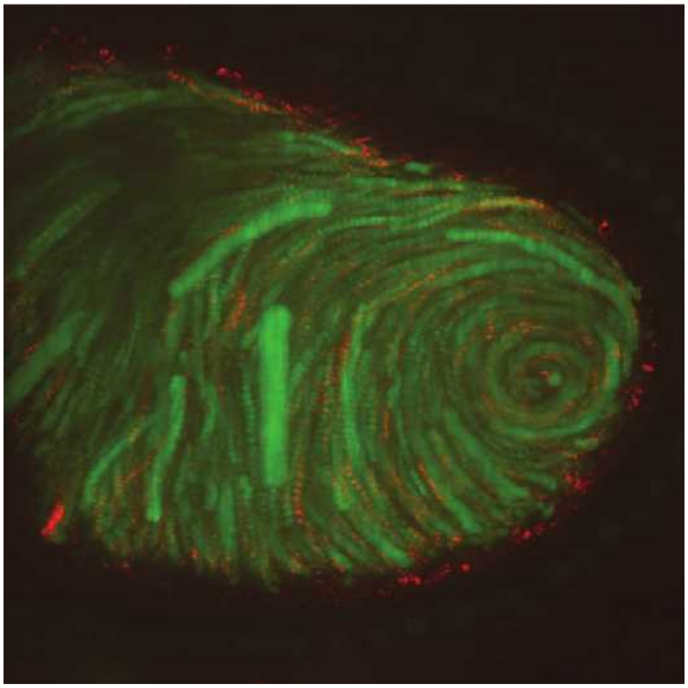

Figure 5.1. Multiple, superimposed images from a movie, showing movements in a fruit fly oocyte (a developing egg). Yolk granules are stained green, and tiny red fluorescent polystyrene beads have been injected into the egg to show the dynamism of flow in the egg body over time.[2]

And a team of biochemists from Duke and Stanford Universities point out how inadequate is our knowledge of the action of biomolecules when all we have is a frozen structure of the sort commonly reported in the literature. “In reality”, they say, “all macromolecules dynamically alternate between conformational states [that is, between three-dimensional folded shapes] to carry out their biological functions”:

> Decades ago, it was realized that the structures of biomolecules are better described as “screaming and kicking”, constantly undergoing motions on timescales spanning twelve orders of magnitude, from picoseconds [trillionths of a second] to seconds (Ganser et al. 2019).

Why, after all, should we ever have expected our physiology to be less a matter of *gesturings* than is our life as a whole?

A long way from crystalline order

According to the old story of the machine-organism, a protein-coding DNA sequence, or gene, is not only mirrored in an exact messenger RNA (mRNA) sequence, but the mRNA in turn is translated into an exact amino acid sequence in the resulting protein, which finally folds into a fixed shape predestined by that sequence. It was a picture of perfect, lawful, lockstep necessity, leading from DNA through mRNA to a final, functional protein.

"There is a sense," wrote Richard Dawkins, "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 read-only memory to precisely invariant three-dimensional protein shape, is a remarkable feat of digital information technology" (Dawkins 2006, p. 171).

And these proteins in turn were thought to carry out their functions by neatly engaging with each other in a machine-like manner, snapping into place like perfectly matched puzzle pieces or inserting into each other like keys in locks.

We now know, and already knew when Dawkins published those words, that everything about this narrative was wrong — and not only the parts about DNA and RNA. Among proteins (those "workhorses of the cell") every individual molecule lives in transformational movement — as a dynamic ensemble of rapidly "morphing", or interconverting, conformations — and therefore does not have a "precisely invariant three-dimensional shape".

But there is much more that wholly escaped Dawkins' computerized imagination.[3] Quite apart from the fact that each protein molecule rapidly shifts between distinctly different, folded structures, we now know that *intrinsically disordered proteins* — proteins that, in whole or in part, have no particular, inherent structure at all — are crucial for much of a cell's functioning. Researchers refer to "fluid-like" and "surface-molten" proteins (Grant et al. 2010; Zhou et al. 1999). This is why biophysicist Konstantin Turoverov and his Russian and American colleagues tell us that "the model of the organization of living matter is changing to one described by highly dynamic biological soft matter". For decades, they note, protein interactions were "considered to be rigid, where, for a given protein, a unique 3D structure defined a unique biological activity". However,

> it is now realized that many protein functions rely on *the lack of specific structure*. This recognition has changed the classical consideration of a functioning protein from a quasi-rigid entity with a unique 3D structure resembling an aperiodic crystal into a softened conformational ensemble representation, with intrinsic disorder affecting different parts of a protein to different degrees[4] (Turoverov et al. 2019, emphasis added).

Clearly, the finally achieved protein need not be anything like the predetermined, inflexible mechanism with a single, well-defined structure imagined by Dawkins. Proteins can be true shape-shifters, responding and adapting to an ever-varying context — so much so that (as the noted experimental cell biologist, Stephen Rothman, has written) 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 (Rothman 2002, p. 265).

Many intrinsically unstructured proteins are involved in regulatory processes, and often serve as Proteus-like hub elements at the center of large protein interaction networks (Gsponer and Babu 2009). They also play a decisive role in molecular-level communication within and between cells, where their flexibility allows them to modulate or even reverse the typical significance of a signal,[5] in effect transforming *do this* into *do that* (Hilser 2013).

But the troubling question arises: if unstructured proteins, or unstructured regions in proteins, are not “pre-fitted” for particular interactions — if, in their “molten” state, they have boundless possibilities for interacting with other molecules and even for reversing their effects — how do these proteins “know” what to do at any one place and time? Or, as one pair of researchers put it, “How is the logic of molecular specificity encoded in the promiscuous interactions of intrinsically disordered proteins?” (Zhu and Brangwynne 2015). In the next section we will look at one of the most recent and dramatic developments in cellular physiology, which has seemed to many biologists to offer an approach to this problem.

But first we should note the continuing mechanistic bias in the negative descriptors, “disordered” and “unstructured”, which I have grudgingly adopted from the conventional literature. Contrary to this usage, 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 the many living processes these proteins harmoniously support and participate in (including, in fact, the movements of the ballet dancer), it would be strange to assume that their performance is anything *less* than graceful, artistic, purposive, and meaningful.

The unexpected phases of life

It has become increasingly clear in recent years that, quite apart from its cytoskeleton and membrane-bound organelles (Chapter 4), the fluid cytoplasm in each cell is elaborately and “invisibly” organized. Various macromolecular complexes and other molecules, in more or less defined mixes, congregate in specific locations and sustain a collective identity, despite being unbounded by any sort of membrane. Here we’re looking at significant structure, or organization, without even a pretense of mechanically rigid form. How do cells manage that?

The problem was framed this way by Anthony Hyman from the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, Germany, and Clifford Brangwynne from the Department of Chemical and Biological Engineering at Princeton University:

> Non-membrane-bound macromolecular assemblies found throughout the cytoplasm and nucleoplasm … consist of large numbers of interacting macromolecular complexes and act as reaction centers or storage compartments … We have little idea how these compartments are organized. What are the rules that ensure that defined sets of proteins cluster in the same place in the cytoplasm?

Even more puzzling, a “compartment” can maintain its functional (purposive) identity despite the rapid exchange of its contents with the surrounding cytoplasm. “Fast turnover rates of complexes in compartments can be found throughout the cell. How do these remain as coherent structures when their components completely turn over so quickly?” (Hyman and Brangwynne 2011).

Well-structured droplets

Part of the picture that has recently come into focus has to do with the phases of matter and the transitions between these phases. (Think, for example, of the solid, liquid, and gaseous phases of water, or of solutions and gels — matter in different states.) For example, it’s possible for well-defined droplets of one kind of liquid to occur within a different liquid, like oil droplets in water.

We now know that molecular complexes containing both RNA and protein often gather together to form distinctive RNA-protein liquids that separate out as droplets within the larger cytoplasmic medium. Like liquids in general, these droplets tend toward a round shape, can coalesce or divide, can wet surfaces such as membranes, and can flow. The concentration of particular molecules may be much greater in the droplets than in the surrounding fluid, conferring specific and efficient functions upon the assemblies.

Enzymes and reactants can rapidly diffuse within the liquid droplet, while also moving with relative ease across the boundary between droplet and surrounding medium. Yet this boundary can remain distinct until phase-changing environmental conditions occur — conditions that might involve slight changes in temperature, pH, salt concentration, electrical charge, molecular densities, the addition of small chemical groups to proteins, degradation of proteins, the activity of gene transcription, or still other factors.

In this way, a very subtle change — originating, say, from an extracellular influence — can yield a dramatic transformation of cytoplasmic organization, just as a slight change in the temperature or salinity of water can shift an ice-forming condition to an ice-melting one, or vice versa.

Moreover, these phase-separated droplets can be highly organized internally: “multiple distinct liquid phases can coexist and give rise to richly structured droplet architectures determined by the relative liquid surface tensions” (Shin and Brangwynne 2017). Also, some parts may become gel-like,[6] and others may form more or less solid granules. Many such droplets may pass through stages, from more liquid to more solid, before dispersing. They form in response to particular needs, perform their work, and then pass away. Others are more or less permanent. Phase separation has been called “a fundamental mechanism for organizing intracellular space” (Shin and Brangwynne 2017) — one where “function derives not from the structures of individual proteins, but instead, from dynamic material properties of entire [protein aggregates] acting in unison through phase changes” (Halfmann 2016).

We also know now that weak, transient interactions among intrinsically unstructured proteins and RNAs can result in crucial, flexible “scaffolds” that help to assemble these phase-separated aggregates, drawing in a set of functionally related molecules. “Weak”, “transient”, and “flexible” in my description here might be taken as indicators of the living, responsive, and non-machine-like character of the activity.

When *things happen* in the cell, phase transitions often play decisive roles, as a University of Colorado group discovered when looking at phase transitions in a roundworm. According to the researchers, these transitions “are controlled with surprising precision in early development, leading to starkly different supramolecular states” with altered organization and dynamics. “Reversible interactions among thousands of [these phase-separated] complexes”, the authors found, account for “large-scale organization of gene expression pathways in the cytoplasm” (Hubstenberger et al. 2013).

How do you regulate flow and phases?

All this is, if you think about it, an amazing departure from the kind of picture once burned into the minds of biologists such as Richard Dawkins, from whom we heard some errant words above. Once there were dreams of compelling digital instructions in DNA; of machine-like interactions between molecules; of deterministic formation and functioning of proteins; of the cell as a collection of cleanly separate, well-defined structures; and of cellular processes with fully predictable outcomes. But this dream has faded in the clear daylight of an entirely different reality where, among many other things, we watch a subtle and almost incomprehensible play of material changes of state.

These state changes can be affected by infinitely varying factors, such as the momentary interaction between a few molecules of a particular sort, the “minor” modification of a molecule, the increasing concentration of molecules in a particular location, or the slight temperature change of a degree or two — the kind of change that, in the larger world of nature, can freeze the surface of a lake where, a few days previously, fish routinely breached the surface to feed on insects.

> Ice cools a drink, water carves a canyon, steam powers a locomotive … But ice brings down power lines, water floods towns, steam scalds skin. The context for these states matters, and there can be consequences if the appropriate state is perturbed or dysregulated. Now more than ever, we understand that physical states dictate biological function, and … recent papers have highlighted, at the subcellular and tissue levels, the importance of understanding those states and the conditions in which they occur. (Szewczak 2019)

We heard it asked earlier how intrinsically unstructured proteins “know” what to do at any one place and time. The old model assumed, rather puzzlingly, that random encounters between freely diffusing molecules accounted for many of the biological interactions we observe. But numerous researchers are now embracing the emerging picture of biological phase transitions as offering a very different understanding. Peter Tompa, a structural biologist from Vrije Universiteit Brussel in Belgium, sees certain phase transitions as directing “the movement of regulatory proteins in and out of organized subcellular domains" — part of the systematic maintenance of order in the cell[8] (Tompa 2013).

This is all well and good, but does it tell us (as is often implied) what "controls" and "directs" molecular engagements in relation to the distinct needs of the cell at different locations and times? If the organization of phase-separated aggregates is what coordinates the activity of proteins, then we shouldn't have to ask, as researchers are now asking, "Why do some proteins localize to only the nucleolus, while others can be found in both the nucleolus and Cajal bodies?" (Zhu and Brangwynne 2015). (Cajal bodies, like the nucleolus, are non-membrane-bound organelles found in the cell nucleus.) And, even if that question had a ready answer, the more fundamental issue would remain: if we assume that phase-separated droplets lead to properly coordinated protein interactions, then what explains the well-timed and intricately organized formation, structuring, and dissolution of the condensates?

Figure 5.2. As an aside: Some researchers have applied the idea of biological phase transitions in a novel way. Certain species of penguins huddle tightly against the fierce cold of the sunless Antarctic winter (top photo), or aggregate in somewhat looser clumps when it is a little warmer (bottom photo), or move about more or less independently when it is warmer still. So the different phases of their interaction are correlated with temperature, just as water varies from solid to liquid to gas, depending (among other things) on the temperature.[7]

This illustrates how (to get ahead of ourselves just a little bit) all attempts to answer questions of regulation in strictly physical terms never do really answer them. Rather, they lead only to an elucidation of previous physical states that again raise the same broad questions. There is no way to step outside the endlessly regressing physical explanations except by truly stepping outside them — except, that is, by turning to the play of intentions and end-directed activities that are implicit in the stories we find ourselves looking at.

After all, questions about biological regulation are questions about the *significant patterning* of living events, and these just *are* questions about a story — about the relation of continually adjusted means to the needs, strivings, and qualities of a particular life. It is no surprise, then, that our answers must be gained in the way we come to understand a story —

not in the way we grasp the play of physical laws in, say, the bodily movements of walking or speaking.

And then there is water — the mediator of flow

I have long thought that some day water will be seen as the single most fundamental, "information-rich" physical constituent of life, and that revelations in this regard will outweigh in significance even those concerning the structure of the double helix. Not many biologists today would countenance such a suggestion, and I am not going to mount a serious defense of it here, if only for lack of ability. Time will decide the matter soon enough. But I was particularly pleased to find that the widely read and respected *Nature* columnist, Philip Ball, once entitled a piece, "Water as a Biomolecule". In it he wrote:

> Water is not simply 'life's solvent', but rather an active matrix that engages and interacts with biomolecules in complex, subtle and essential ways … Water needs to be regarded as a protean, fuzzily delineated biomolecule in its own right (Ball 2008a; see also Ball 2008b.)

In another paper, Ball (2011) summarized some work bearing on the role of water in biological contexts. The main topic had to do with the relation between water, the binding cavity of an enzyme, and the substrate molecule to which the enzyme binds. It turns out, according to the authors of a study Ball cites, that "the shape of the water in the binding cavity may be as important as the shape of the cavity". Ball goes on to remark:

> Although all this makes for a far more complicated picture of biomolecular binding than the classic geometrical "lock and key" model, it is still predicated on a static or quasi-equilibrium picture. That, too, is incomplete.

Then he cites another paper on enzyme-substrate binding. There it is revealed that, before the binding is complete, water movement near the enzyme is retarded. "Crudely put, it is as if the water 'thickens' towards a more glassy form, which in turn calms the fluctuations of the substrate so that it can become locked securely in place. It is not yet clear what causes this solvent slowdown as a precursor to binding; indeed, the whole question of cause and effect is complicated by the close coupling of protein and water motion and will be tricky to disentangle. In any event, molecular recognition here is much more than a case of complementarity between receptor and substrate — it also crucially involves the solvent".

All this suggests to Ball that "changes in protein and solvent dynamics are not mere epiphenomena, but have a vital role in substrate binding and recognition".

Structural biologists Mark Gerstein and Michael Levitt (the latter a 2013 Nobel laureate in chemistry) wrote a 1998 article in *Scientific American* entitled "Simulating Water and the Molecules of Life". In it they mentioned how early efforts to develop a computer simulation of a DNA molecule failed; the molecule (in the simulation) almost immediately broke up. But when they included water molecules in the simulation, it proved successful. "Subsequent simulations of DNA in water have revealed that water molecules are able to interact with nearly every part of

DNA's double helix, including the base pairs that constitute the genetic code" (Gerstein and Levitt 1998).

Early attempts to simulate protein molecules rather than DNA produced an analogous difficulty, with the same, water-dependent resolution. Gerstein and Levitt concluded their article with this remark:

> When scientists publish models of biological molecules in journals, they usually draw their models in bright colors and place them against a plain, black background. We now know that the background in which these molecules exist — water — is just as important as they are.

That was in 1998. More than twenty years later the background remains to be filled in, even if we are now seeing signs of change. Philip Ball (who likes to cite that Gerstein/Levitt remark, and who reproduces two images like the one in Figure 5.4) has recently noted "an interesting sociological question", namely, "why certain communities in science decide that particular aspects of a problem are worth devoting a great deal of attention to while others become minority concerns, if not in fact regarded as somewhat suspect and disreputable". He adds:

> Why should we place so much emphasis, for example, on determining crystal structures of proteins and relatively little on a deep understanding of the [water-related] forces … that hold that structure together and

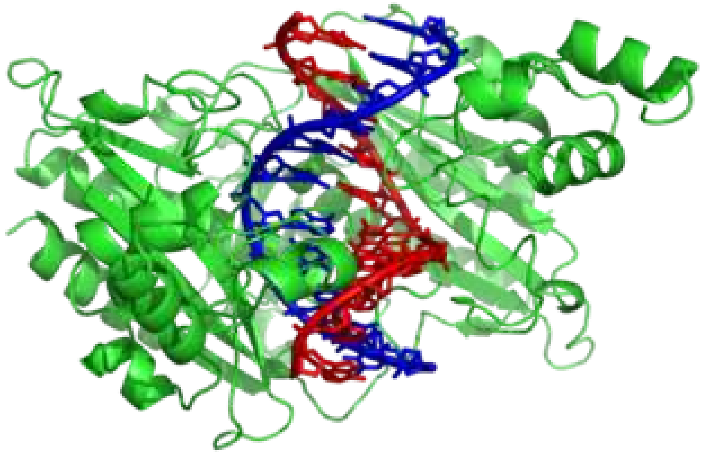

Figure 5.3. A typical "ribbon" diagram of a protein, representing certain basic structural elements.[9]

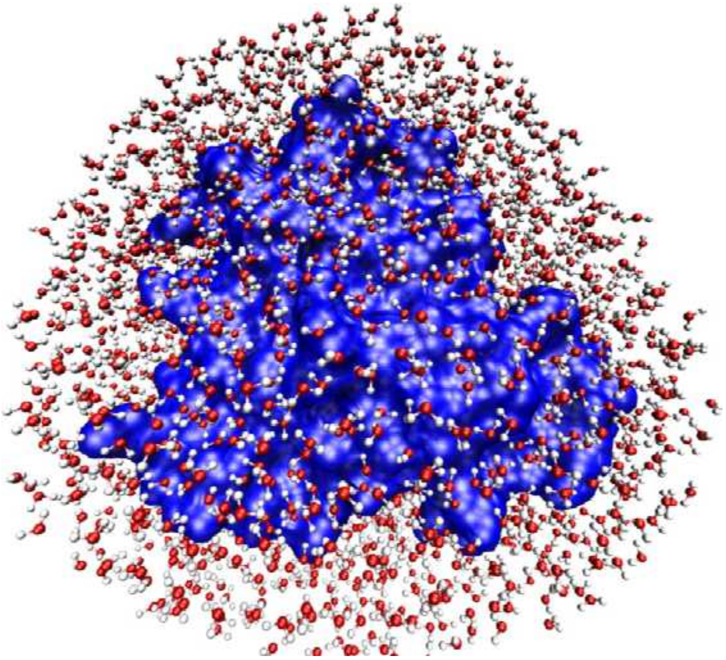

Figure 5.4. A representation of a protein's hydration shell, where the small, red-and-white figures stand for water molecules. Of course, both this and the preceding image represent almost nothing of the reality of the molecules (whatever we might take that reality to be), but only certain abstractly conceived features.[10]

> that enable it to change and flex so that the molecule can do its job? (Ball 2013)

Certain peculiar historical episodes have contributed to the disreputability of water as a “molecule of life”. (Too many researchers have thought they glimpsed something about water that went beyond current principles of understanding, so that work of this sort came to be seen as mystically tainted or “on the fringe”.) But surely part of the answer to Ball’s question has to do with the longstanding distortion of biology due to the emphasis upon code and mechanism. It is much easier to imagine the step-by-step execution of a computer-like code or the clean insertion of a key into a lock than it is to come to terms with fluid transformations — that is, with what is actually life-like.

The high era of molecular biology that followed upon discovery of “the” structure of the double helix was indeed the Age of Simplicity. We can be thankful that the feverish enchantment of code and crystal is now giving way to an increasing recognition of movement, flow, dynamically flexible interaction, and the continual transfiguration of form — prime narrative elements in the organism’s story.

Where are we now?

Organisms Are Activities, Not Things

Many observers have sensed, whether vividly or dimly, that the modern fixation upon things rather than activities — on what has already become rather than the process of becoming — severely distorts our sense of reality. But it is hard for us today to step fully out of this distortion. And nowhere is that distortion more destructive than in the science of life.

Perhaps for that very reason the distortion is also more visible in the science of life. And thanks to new imaging technologies, the visibility is quite literal. At the cellular level, novel techniques are enabling us to see not only frozen, crystallized structures, but live movement. DNA, RNA, and proteins are being reconceived as "biological soft matter", subject to continually changing form so that molecular performances become more like improvised dances than automatic lock-and-key mechanical interactions. "Disordered" or "unstructured" sequences in proteins are now seen as decisive for coordinated activities throughout the cell, from gene regulation to signaling across membranes.

Still more dramatically, molecular biologists have in recent years become almost transfixed by the novel importance of phase transitions — for example, the forming and dissolving of distinctive, membraneless droplets within the fluid cell, whereby specialized and localized functional capacities are maintained despite the rapid passage of molecules in and out of the droplets.

And perhaps most important of all is the nascent recognition — which still hasn't taken widespread hold in biology — that the amazing functional plasticity of water may be key to just about everything that goes on in a cell.

All this points us to the question of coherence: how are the virtually infinite "degrees of freedom", so evident in the free flows of the cell, disciplined and subordinated to the larger purposes of the cell, whether they be gene expression or intercellular communication or metabolism or cell division. In the next chapter ("Context: Dare We Call It Holism?") and in Chapter 8 ("The Mystery of an Unexpected Coherence") we will try to get some clearer views of this larger, meaningful picture.

Notes

1. For examples of how the movement of blood structures the heart and blood vessels, see the section on "becoming" in Chapter 25.

2. Figure 5.1 credit: Copyright Margot Quinlan. Reproduced with permission.

3. In Chapter 8 we will look at *alternative splicing* of RNAs, one of many ways the DNA sequence is radically overridden by the larger purposes of the cell.

4. A terminological issue: Turoverov and colleagues speak more specifically of “highly dynamic biological soft matter positioned at the edge of chaos”. The abstract and perhaps rather tiresome notion of “the edge of chaos” is better captured in this context by a picture of lifelike processes — powerfully organized, but in a dynamic manner that continually adapts to circumstances from a purposive, and therefore not *physically* predictable, center of agency. The predictability, such as it is, lies in the reasonable expectation of coherence in the interweaving meanings we observe. (See Chapters 2 and 8.

5. Biologists often speak of communication in terms of *signals* and *signaling*, where *signal* can hardly be distinguished in any absolute way from *cause*. However, “signals” tend to be spoken of where there are repeated, more or less stereotypical sequences (“pathways”) of molecular interaction between different cells, leading to more or less consistent consequences. This happens, for example, when a gland secretes a hormone (“signal”) that subsequently has effects in other parts of the body.

Wikipedia offered this definition of “cell signaling” in August, 2019: “Cell signaling is part of any communication process that governs basic activities of cells and coordinates multiple-cell actions. The ability of cells to perceive and correctly respond to their microenvironment is the basis of development, tissue repair, and immunity, as well as normal tissue homeostasis”. This easy acknowledgment of “communication”, “coordination”, “governance”, “perception”, and “correct response” — all within a science that, on the surface, refuses the normal and unavoidably immaterial meaning of these terms — illustrates the biologist’s blindsight described in Chapter 1.

6. A sol-gel transition occurs when a solution (in which one substance is dissolved in another) passes into a gel state. The latter consists of a solid molecular lattice that is expanded throughout its volume by a fluid — water, in the case of a hydrogel. The fluid may constitute over 99% of the volume of the gel, yet the solid lattice prevents the gel from flowing like a liquid.

7. Figure 5.2 credit: from Gerum et al. 2013 (CC BY-SA 3.0).

8. Here is one of innumerable examples of the role of phase separation in physiological processes: “Cells under stress must adjust their physiology, metabolism, and architecture to adapt to the new conditions. Most importantly, they must down-regulate general gene expression, but at the same time induce synthesis of stress-protective factors, such as molecular chaperones … [We] propose that the solubility of important translation factors is specifically affected by changes in physical–chemical parameters such [as] temperature or pH and modulated by intrinsically disordered prion-like domains. These stress-triggered changes in protein solubility induce phase separation into aggregates that regulate the activity of the translation factors and promote cellular fitness” (Franzmann and Alberti 2019).

9. Figure 5.3 credit: © Richard Wheeler (GNU FDL).

10. Figure 5.4 credit: From Frauenfelder 2009.

Sources

Ball, Philip (2008a). “Water as a Biomolecule”, *ChemPhysChem* vol. 9, pp. 2677-85. doi:10.1002/cphc.200800515

Ball, Philip (2008b). “Water as an Active Constituent in Cell Biology”, *Chemical Reviews* vol. 108, no. 1, pp. 74-108. doi:10.1021/cr068037a

Ball, Philip (2011). “More Than a Bystander”, *Nature* vol. 478 (October 27), pp. 467-68. doi:10.1038/478467a

Ball, Philip (2013). “Concluding Remarks: *Cum Grano Salis*”, *Faraday Discussions* vol. 160, pp. 405–14. doi:10.1039/c2fd20126g

Dawkins, Richard (2006). *The Blind Watchmaker*, third edition. New York: W. W. Norton. First edition published in 1986.

Franzmann, Titus M. and Simon Alberti (2019). “Protein Phase Separation as a Stress Survival Strategy”, *Cold Spring Harbor Perspectives in Biology* vol. 11, no. 6 (June). doi:10.1101/cshperspect.a034058

Frauenfelder, Hans, Guo Chen, Joel Berendzen et al. (2009). “A Unified Model of Protein Dynamics”, *PNAS* vol. 106, no. 13 (March 31), pp. 5129-34. https://doi.org/10.1073/pnas.0900336106

Ganser, Laura, Megan L. Kelly, Daniel Herschlag and Hashim M. Al-Hashimi (2019). “The Roles of Structural Dynamics in the Cellular Functions of RNAs”, *Nature Reviews Molecular Cell Biology* (Aug). doi:10.1038/s41580-019-0136-0

Gerstein, Mark and Michael Levitt (1998). “Simulating Water and the Molecules of Life”, *Scientific American* vol. 279, no. 5 (November), pp. 100-5. doi:10.1038/scientificamerican1198-100

Gerum, R. C., B. Fabry, C. Metzner et al. (2013). “The Origin of Traveling Waves in an Emperor Penguin Huddle”, *New Journal of Physics* vol. 15 (December). https://iopscience.iop.org/article/10.1088/1367-2630/15/12/125022

Grant, Barry J., Alemayehu A. Gorfe and J. Andrew McCammon (2010). “Large Conformational Changes in Proteins: Signaling and Other Functions”, *Current Opinion in Structural Biology* vol. 20, pp. 142-47. doi:10.1016/j.sbi.2009.12.004

Gsponer, Jörg and M. Madan Babu (2009). “The Rules of Disorder Or Why Disorder Rules”, *Progress in Biophysics and Molecular Biology* 99, no. 2-3 (February-May), pp. 94-103. doi:10.1016/j.pbiomolbio.2009.03.001

Halfmann, Randal (2016). “A Glass Menagerie of Low Complexity Sequences”, *Current Opinion in Structural Biology* vol. 38, pp. 18-25. doi:10.1016/j.sbi.2016.05.002

Hilser, Vincent J. (2013). “Structured Biology: Signalling from Disordered Proteins”, *Nature* vol. 498 (June 20), pp. 308-10. doi:10.1038/498308a

Hyman, Anthony A. and Clifford P. Brangwynne (2011). “Beyond Stereospecificity: Liquids and Mesoscale Organization of Cytoplasm”, *Developmental Cell* vol. 21 (July 19), pp. 14-16. doi:10.1016/j.devcel.2011.06.013

Hubstenberger, Arnaud, Scott L. Noble, Cristiana Cameron and Thomas C. Evans (2013). “Translation Repressors, an RNA Helicase, And Developmental Cues Control RNP Phase Transitions during Early Development”, *Developmental Cell* vol. 27 (October 28), pp. 161-73. doi:10.1016/j.devcel.2013.09.024

Landecker, Hannah (2012). “The Life of Movement: From Microcinematography to Live-Cell Imaging”, *Journal of Visual Culture* vol. 11, pp. 378-99. doi:10.1177/1470412912455622

Pearson, Helen (2003). “Beyond the Double Helix”, *Nature* vol. 421 (January 23), pp. 310-12. 10.1038/421310a

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

Shin, Yongdae and Clifford P. Brangwynne (2017). “Liquid Phase Condensation in Cell Physiology and Disease”, *Science* vol. 357, no. 6357 (September 22). doi:10.1126/science.aaf4382

Szewczak, Lara (2019). “Just Solid or Liquid Enough”, *Cell* vol. 178, no. 4 (August 8), pp. 763-64. doi.org/10.1016/j.cell.2019.07.027

Tompa, Peter (2013). “Hydrogel Formation by Multivalent IDPs: A Reincarnation of the Microtrabecular Lattice?”, *Intrinsically Disordered Proteins* 1:e24068 (January–March). doi:10.4161/idp.24068

Turoverov, Konstantin K., Irina M. Kuznetsova, Alexander V. Fonin et al. (2019). “Stochasticity of Biological Soft Matter: Emerging Concepts in Intrinsically Disordered Proteins and Biological Phase Separation”, *Trends in Biochemical Sciences* vol. 44, no. 8 (August 1), pp. 716-28. https://doi.org/10.1016/j.tibs.2019.03.005

Zhou, Yaoqi, Dennis Vitkup and Martin Karplus (1999). “Native Proteins Are Surface-Molten Solids: Application of the Lindemann Criterion for the Solid versus Liquid State”, *Journal of Molecular Biology* vol. 285, pp. 1371-1375. doi:10.1006/jmbi.1998.2374

Zhu, Lian and Clifford P. Brangwynne (2015). “Nuclear Bodies: The Emerging Biophysics of Nucleoplasmic Phases”, *Current Opinion in Cell Biology* vol. 34, pp. 23-30. doi:10.1016/j.ceb.2015.04.003

Chapter 6

Context: Dare We Call It Holism?

The centrality of living wholes within biology seems beyond argument. These have not been "put together" or built by an external agency. They are never the *results* of a physical activity that starts with non-wholes. Biology gives us nothing but beings that have never existed except as wholes possessing the formative powers that enable them to pass through further stages of physical development.

The one-celled zygote is already a functioning whole. It does not gain further cells through the addition of "building blocks" assembled by an engineer or designer, but rather through an internal power of reorganization and subdivision in which the entire organism participates. All the parts are orchestrated in a unified performance that yields (through division of existing cells) new cells, and particular kinds of cells, just where they are needed. The orchestrating power of the whole can hardly be determined by the particular parts it in this way brings into being and orchestrates.

Where the physicist may prefer unambiguous, isolated, and well-defined "point" causes, the biologist never has such causes to theorize about. A biological whole is never absolute, and never perfectly definable as distinct from its environment. Further, its actions are always multivalent, like the meaning of a sentence in a profound and complex text. Its activities interpenetrate one another, like the events of a story.

The wonderfully insightful twentieth-century botanist, Agnes Arber (Arber 1985, p. 59), captured well the polar tension between organic wholeness, on one hand, and contextual embeddedness, on the other:

> The biological explanation of a phenomenon is the discovery of its own intrinsic place in a nexus of relations, extending indefinitely in all directions. To explain it is to see it simultaneously in its full individuality (as a whole in itself), and in its subordinate position (as one element in a larger whole).

Every ecological setting, every organism within that setting, every organ within the organism, and every cell within the organ is a whole providing a context for its own interrelated parts, and at the same time is itself contextually embedded within larger wholes. "Context", "whole", and "part" can never be rigid, absolute terms in biology. They are bound up with interweaving spheres of activity.

We need to gain some practice in thinking, not with the single, distinct point-causes of the physicist (or at least the classically minded physicist), but rather with the actual narrative qualities of biological activity. The perplexing issues surrounding attempts at holistic thought may thereby lend themselves more easily to our efforts at understanding.

Which comes first, the cell or its niche?

Every cell in an organism lives in a sufficiently distinctive way — is enough of a whole in its own right — to pose the question of identity. What makes this particular cell of my skin a keratinocyte rather than a melanocyte? Does identity imply constancy of cellular character? To what degree does a cell's environment — the larger community of cells — shape its identity and character?

Current researches are showing us how the fate of any given cell in our bodies is bound up with that of nearby cells in the same local environment, or "niche".[1] Consider, for example, the basal stem cells of the mammalian airway. (*Basal cells* are epithelial cells constituting the lowest layer of epidermis, and *stem cells* are relatively undifferentiated cells capable, at need, of dividing and differentiating into more specialized cell types.)

One research group found that when airway basal stem cells were in demand as a result of injury, there was a "surprising increase in the proliferation of committed secretory cells". It turned out that many of these latter, fully differentiated (specialized) cells, were, so to speak, reversing their specialization and becoming basal stem cells. The "de-differentiated" cells "were morphologically indistinguishable from stem cells and they functioned as well as [normal stem cells] in repairing epithelial injury … This capacity of committed cells to de-differentiate into stem cells may have a more general role in the regeneration of many tissues" (Tata et al. 2013).

Further, direct contact with a single basal stem cell was enough to prevent secretory cells from de-differentiating and becoming stem cells. Clearly, then, the identity of these fully matured secretory cells is not rigidly fixed, and at the same time their transformation potential is delicately sensitive to context. We can hardly separate the question of a cell's identity from that of the niche's identity, or from the changing needs of the moment.

This point is driven home by a second study concerning mouse hair follicles.[3] The researchers explored how a cell's location within various compartments of the niche affects its fate. For example, stem cells in the bulge (see Figure 6.1) tend to stay quiescent — that is, they remain in a resting state without cell division — whereas those in the hair germ are continually differentiating into more specialized cell types. And even within the bulge, stem cells in the upper half remain much more consistently quiescent, whereas those in the lower half are more proliferative.

Dramatically, the authors also show that "hair follicle stem cells are dispensable for regeneration, and that epithelial cells, which do not normally participate in hair growth, re-populate the lost stem-cell compartment and sustain hair regeneration" — provided, however, that "the overall integrity of the niche is maintained". When the stem cell population in the bulge or hair germ is destroyed by laser ablation, distant epithelial cells flow toward the damaged compartment and go through a transformation of identity enabling them to replace the lost cells. As the authors summarize it, "The overall structure and function of the tissue is maintained because cells are capable of adopting new fates as dictated by their new niche microenvironment".

Clearly, the different elements of the hair follicle niche are not rigidly fixed entities. Rather, their changing forms and relationships are choreographed by the larger environment. So the goings-on in the hair follicle illustrate very well how the context helps to "decide" what sorts of elements it will have, how they will be formed and transformed, and how they will come into mutual relationship. Nothing could be further from the common picture of an organism being constructed, bottom-up, from an available collection of well-defined building blocks capable of determining outcomes.

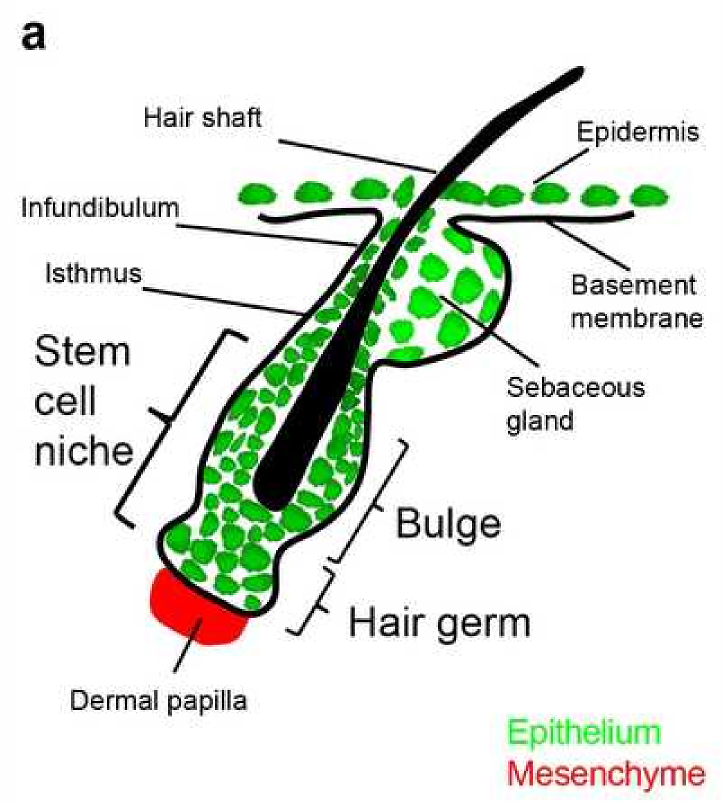

Figure 6.1. Mouse hair follicle.[2]

And we need to remember that the humble hair follicle represents just one of millions of distinct niches within a mouse or human being. Liver, kidney, heart — every organ embraces countless micro-environments, none of which is exactly like any other. In every one of those micro-environments a unique, evolving collection of cells is caught up in the wholeness of its governing context. And the same demand for flexible coordination, but now at a higher level, is repeated as all those niches are assimilated to the unity of a single organ, and again in the way the organs are brought into harmony within the functioning of the whole organism.

Embryos in general exhibit this power of flexible coordination to an extraordinary degree. Harvard biologist Richard Lewontin once described how you can excise the developing limb bud from an amphibian embryo, shake the cells loose from each other, allow them to reaggregate into a random lump, and then replace the lump in the embryo. A normal leg develops. Somehow the form of the limb as a whole is the ruling factor, redefining the parts according to the larger pattern. Lewontin went on to remark:

> Unlike a machine whose totality is created by the juxtaposition of bits and pieces with different functions and properties, the bits and pieces of a developing organism seem to come into existence as a consequence of their spatial position at critical moments in the embryo's development.

A developing organism, Lewontin adds, “is like a language whose elements … take unique meaning from their context” (Lewontin 1983).

‘More than the sum of its parts’: resurrecting a cliché

The foregoing illustrates how a biological context defines its parts — lends them their meaning — not the other way around. However hard it may be for us to conceive, there seems to be something fundamentally *causal* about a context. It *governs* its parts, bringing them into existence, transforming them, and coordinating their activity. But there is another, closely related way to look at the matter. For this we can turn to the preeminent cell biologist, Paul Weiss, whose work extended from the 1920s into the 1970s, when he was awarded the National Medal of Science by President Jimmy Carter.

As a life-long observer of cells and tissues, Weiss pointed out something obvious, simple, and yet revolutionary for today’s biology. When we examine the form and physiology of an organism, we see how “certain definite rules of order apply to the dynamics of the *whole* system … reflected [for example] in the orderliness of the overall architectural design, which cannot be explained in terms of any underlying orderliness of the constituents” (Weiss 1971, p. 286).

That is, despite the countless processes going on in the “heaving and churning” (Weiss 1973, p. 40) interior of 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 come 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 (Weiss 1962, p. 6).

Tuning in to this basic picture — if we could really take it seriously — might change just about everything in biology. It is therefore worth hearing the voice of one other competent authority who emphatically echoed Weiss’ remarks, despite writing from a very different specialist’s angle. In a 1985 paper Guenter Albrecht-Buehler, a biophysicist at Northwestern University, wrote this:

> During the course of uncountable simultaneous biochemical and biophysical events, information is copied, received, transmitted, and stored as hormones, mRNAs, neurotransmitters, pre- and postsynaptic potentials, post-translational modifications, covalent links between macromolecules. Different kinds of cyclic events keep time and synchronize other cellular events, eventually generating mitotic cycles and circadian rhythms. Materials such as proteins and RNAs or much larger structures such as viruses or organelles that carry the information around are transported, produced, exchanged, recycled, modified, inhibited, or stored.

And he concluded: “All these events occur in a microscopically small world of violent and random thermal fluctuations. Yet, cytoplasm can keep its complex actions accurate in the midst of drowning thermal noise all around and within” (Albrecht-Buehler 1985).

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, given the untethered freedom of its molecular constituents as they make their way through a watery medium.

The same principle holds when we look at the “erratic” placement of individual cells within a larger tissue that exhibits beautiful order. In Weiss’ summary:

> While the state and pattern of the whole can be unequivocally defined as known, the detailed states and pathways of the components not only are so erratic as to defy definition, but, even if a Laplacean spirit[4] could trace them, would prove to be so unique and nonrecurrent that they would be devoid of scientific interest.

“This”, Weiss remarks, “is exactly the opposite of a machine”, where the pattern of the product “is simply the terminal end of a chain of rigorously predefined sequential operations of parts. In a [biological] system, the structure of the whole coordinates the play of the parts; in the machine, the operation of the parts determines the outcome” (Weiss 1973, p. 41).

Everything here might well remind us of what we heard from E. S. Russell in Chapter 2: in living activity, the end is more constant than the means. Or: the *purposive* end is more constant than the *physical* means. And it can hardly be disputed: the imposition of order upon the cell that we have been describing seems impossible to understand without an element that looks much more like intention than like the physical lawfulness through which that intention realizes itself. (As I have tried to make clear since the first chapter of this book, and hope to make clearer still in what follows, I am not necessarily speaking of human-like awareness, planning, and intention.)

So, anyway, it turns out, with a touch of irony, that *less* change is what shows the whole cell, or any organic whole, to be *more* than the sum of its parts. It’s as if there were an active, coordinating agency subsuming all the part-processes and disciplining their separate variabilities so that they remain informed by, and caught up in, 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, causal parts.

So 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.

Every biological context is a a complex of embodied ideas

Curiously, “holism” has almost become a dirty word in biology. It commonly signifies loose thinking, vagueness, obscurantism, and perhaps even an unfortunate tendency toward mysticism. I say “curiously” because the fact is that biologists speak incessantly about holism. You might almost think they were, in recent years, becoming fanatical about it. It’s just that they prefer to honor holism under the more acceptable slogan, “context matters”. This latter idea occurs like a mantra in the contemporary technical literature, so that it would be hard to find any physiological or behavioral process that is not routinely (and rightly) said to be “context-dependent” or “context-specific”.[5]

Strangely, despite their almost universal employment of the pregnant term “context”, biologists rarely if ever bother to define it or to examine the meanings implicit in their use of it. Intentionally or otherwise, this protects them from an unwelcome meaning. For the word can hardly mean anything at all if it is not a close synonym for “larger whole”. The frequent appeal to context as a decisive determining factor, then, looks rather like an under-the-table invocation of the unmentionable concept of holism. It allows biologists to import the seemingly inescapable idea of the causal whole into their descriptions and theorizing, while outwardly pursuing a style of explanation that pretends to disdain holism in favor of purely physical analysis into parts — the parts whose sum supposedly gives us the whole.

Let’s not forget: when we say that what happens in a cell is “context-dependent”, we are talking about a watery expanse populated by untold billions of molecules in unsurveyable variety. The need is for just the right combinations of molecules to do just the right things “in the moment” — and to do them *in light of the overall state of the entire cell within its particular tissue*. Is this cell just now committing itself to cellular division? Then what these molecules here and those molecules over there must do is now being radically redefined. Their new “assignments” depend not only on their location in the cell, but also on their necessary functional participation in lengthy, complex, temporal sequences of interaction that require the choreographing of countless other molecules as well.

Something is always going on contextually, and all the molecular interactions, taken together, must reflect whatever that something happens to be — must reflect the meaning of the encompassing narrative.

Appeals to context are necessary because transient local causes are unable to explain the purposive and narrative *significance* of whatever is going on. A broader, orchestrated performance is always playing out — a performance to which local processes are made to conform. This seems to imply that a kind of cause is being directed from the context, or whole, toward the parts. (See Chapters 9 and 10 — and especially the section, “The problem of organic form”, in Chapter 12.) The parts, being *caught up* in the form and activity of the larger context, receive from it their shifting identities and meanings.

The word *context* refers etymologically to that which has been *woven together*, and is commonly applied today to language, thought, and intention, and specifically to the connections that weave through meaningful conceptual expression, making a coherent whole out of it. But, whether we have recognized it or not, this meaning remains precisely the same when the word is used in biology. Narrative connections of language, thought, and intention are what make a biological context the characteristic whole that it is, lending it its form and meaning.

All this may be easier to grasp by looking at our own experience.

The activity on and around a football field during a game differs as a context from the activity on and around a baseball field. The difference could neither exist nor be articulated if it weren't for the distinct *ideas* and *intentions* establishing the two contexts, including all the rules of the games, the organization of leagues into teams, and the competitive framework. Those ideas and intentions enable us to predict the kinds of activity we will observe. And the predictions are possible because, one way or another, the activities occur with implicit reference to the ideas. The physical facilities, the

Box 6.1

Some Call It Holism

The yearning for a means to recognize and understand the whole organism seems to have surfaced with more or less intensity throughout all of modern history — but perhaps at no time more insistently and wisely than during the first half of the twentieth century. The great neurosurgeon, Kurt Goldstein, wrote in his masterpiece, *The Organism*, first published in 1934:

> By virtue of [an] isolating, dismembering procedure one can readily abstract and single out from living phenomena those phenomena on the physico-chemical "plane." But the attempt to reintegrate the elements thus abstracted, to reorganize these split-off segments into the reality of living nature, is doomed to fail. … it is not possible to comprehend the whole on the basis of the parts (Goldstein 1995, p. 378).

Likewise, the leading embryologist, F. R. Lillie, wrote in 1906:

> Cells are subordinate to the organism, which produces them, and makes them large or small, of a slow or rapid rate of division, causes them to divide, now in this direction, now in that, and in all respects so disposes them that the latent being comes to full expression … The organism is primary, not secondary; it is an individual, not by virtue of the cooperation of countless lesser individualities, but an individual that produces these lesser individualities on which its full expression depends (quoted in Russell 1930, pp. 243-44).

The eminent physiologist, John Scott Haldane:

> When we endeavour to treat physiological phenomena as separable events we only reach unintelligible chaos to which there is no end. When we seek to understand them as manifestations of life regarded as a whole we find that we can make them intelligible and predictable (Haldane 1931, p. 69).

The mathematician and student of form, D'Arcy Thompson:

> We tend, as we analyze a thing into its parts or into its properties, to magnify these, to exaggerate their apparent independence, and to hide from ourselves (at least for a time) the essential integrity and individuality of the composite whole (Thompson 1917, p. 712).

And, finally, the neurophysiologist Sir Charles Sherrington:

> The living creature is fundamentally a unity. In trying to make the "how" of an animal existence intelligible to our imperfect knowledge, we have, for purposes of study, to separate its whole into part-aspects and part-mechanisms, but that separation is artificial. It is as a whole, a single entity, that the animal, or for that matter the plant, is finally and essentially to be envisaged (quoted in Russell 1930, p. 166).

There are countless other examples of the same sort. And today we see a resurgent defense of holism in some quarters. But I think it is fair to say that the proponents of holism have yet to make their point in a way that faces up to all the issues and effectively communicates these to the larger scientific community. And two of the key issues, which will figure in later chapters, are (1) the necessity to speak of causes other than physical ones, and (2) the role of idea, or thought, in the phenomena of life.

equipment, and the players — all the activities, viewed physically — do not *produce* the ideas; rather, the activities are *governed* by the ideas. Even the very same physical checkerboard differs as a context, depending on whether the governing ideas are those of checkers or chess.

When a player runs from first base toward second and the catcher throws the ball to the second baseman, we understand the narrative sense of it because we understand the relevant ideas and intentions. Similarly, when we say that the fate of two nearly identical cells will diverge radically depending on their locations in the hair follicle niche, or that a particular chromosomal modification is “cell-type-specific” — neuron or muscle cell? — we have in mind the distinct *character* of the different contexts, their unique ways of being, and what they *need* in order to proceed through their different stories within the still larger context of the organism as a whole.

And so — as we already saw in Chapter 2 — whenever we speak of beings rather than things, we necessarily turn to a language of directed intention (*respond*, *develop*, *adapt*, *regulate*, and so on); a normative and aesthetically colored language (everything relating to health and disease, order and disorder, rhythm and dysrhythmia, harmony and disharmony, error and error correction); and a language of wholeness (*context*, *coordination*, *integration*, *organization*).

Not surprisingly, then, the biologist finds herself directly invoking the language of meaning in terms such as *message*, *information*, *communication*, and *signal*. But, again, she usually tries to do so in a mathematized, *de-meaned* manner intended to conceal the inwardness of the organism. Yet her recourse to the ubiquitous idea of context is a dead giveaway: if the word does not signify an ideational, aesthetic, and directive coherence, it refers to nothing living at all. Things just “being there” without expressing an active ideational unity — without a role in a story that matters — do not make a living context.[6]

Contextual wholes and living narratives

We saw in "The Organism's Story" that every animal's life has a narrative quality through which the meanings of its life are expressed. It pursues its own needs and interests; it interprets, responds to, and re-shapes its environment; and it exhibits a certain biological end-directedness or purposiveness in its activity, from the molecular level on up. It is always "up to something" or "going somewhere".

So long as we are content to look only at the sum of physical causes, we miss this narrative. The same would be true if we read a novel while attending only to the physical causes underlying all the events. If we then said that the unbroken connection of these causes proves the absence of the narrative — the absence of the meaningful living activity and the ideas that the story is actually *about* — then we would merely be asserting our fierce determination to see nothing but physical causes.

At this point the reader, perhaps growing impatient, has every right to ask: "If the organism's life is a narrative in the sense you speak of, then who is the narrator? And how does that narrator achieve its 'governing' or 'coordinating' role — if, indeed, you are not suggesting some sort of vital force?"

These are essential questions, and in this chapter I have tried to take the first steps toward an answer. We have seen (in Chapter 2) that biologists in general, despite the "fierce determination" just referred to — and however unconscious they are of the meanings of their words — compulsively refer to organic *contexts* as if they somehow possessed governing powers, and as if organisms really *are* engaged in purposive, or end-directed, activity. So it appears that the questions are not only mine. They are endemic to biology. Whose are the ends or purposes we find ourselves recognizing in the life of an animal?

On my part, I have tried to begin an answer with two basic recognitions. One is that every context, so far as it is a unitary and integral whole, just *is* regarded, for practical explanatory purposes, as the narrator of the story being enacted within its own domain. It informs its parts and disciplines their activity in harmony with the needs and character of the whole. If there seems to be something *causal* about this disciplinary power (and there certainly does), it differs in some respects from the causation we are familiar with in the inanimate world.

One difference is that this biological causation can never be understood in absolute and unambiguous terms. As when reading a novel, we find that unfolding events make ever clearer sense out of an organism's life. But the interwoven and qualitative *reasons* for things never have the simple character of a mathematical law. Moreover (as we heard from Agnes Arber at the outset of this chapter), every causal context is embedded in still larger contexts, without which it cannot be fully understood. Biological causes always interpenetrate one another.

The second key recognition is that a living context, or whole, exists only by virtue of a certain "inwardness" — an inwardness associated with ideas and intentions, and therefore with volition, cognition, and intelligence. This inwardness may not sit well with the prevailing materialism in today's biology, but we will find in Chapter 12 (the section on "The problem of organic form") that it gives us the key for understanding how a context might be said to *causally govern* its constituent elements.

But even before further explanation, the tantalizing fact remains: every activity with a narrative character shares at least one thing with a human-written novel: it has its own immaterial causal basis, or meaning, which alone enables us to understand and explain what is going on. This remains true even if the meanings at issue are radically different between, say, a giraffe and a politician. An implicit belief in the meaning of organic activity is what leads biologists to classify their research projects according to the significant performances of organisms — from gene expression and cell division to pursuing prey and protecting the young.

Calling these activities "functions" may be more comforting to some (because less alive and more machine-like), but what we denote by a function typically just *is* a meaningful performance — a form of contextualized self-expression or self-realization. We would never in the same way say of a volcano that it is *expressing* or *realizing* its own nature in response to its perception of its surroundings.

Meanings require, and are given by, contexts. It seems way past time in biology not only to implicitly recognize the contextual meanings of biological activity, but also to say a conscious "yes" to them and thereby free ourselves to consider the difference between understanding the animate and inanimate worlds.

WHERE ARE WE NOW?

Seeing the Organism in Context

In Chapter 2 the organism's life was described as story-like in the sense that it is a progressive unfolding in time of interwoven meanings expressing the needs, interests, and intentions representing a particular way of being. These meanings cease to exist, as we noted using a dog as an example, at the moment of death.

From there we went on to Chapter 3, where we learned about the all-but-incomprehensible skill and wisdom with which a cell manages its own genome, and to Chapter 4, where this same sort of skill and wisdom finds its expression in connection with the cytoskeleton and cellular membranes.

Then, in Chapter 5, we learned how all this happens in the plastic context of the cell, where organizing powers are reflected in the "dance" of chromosomes, in "molten" regions of proteins, in continual phase transitions in the cellular plasm, and, more generally, in a free movement of molecules within the fluid cell. We saw (with the help of Paul Weiss) that this relatively disordered movement seems in conflict with the overall order of the cell, which is imposed as if "from above".

All this led us to our present concern with the *governing* role of contexts with respect to their parts — "governing" in the sense of imposing order and meaning upon the collective parts and, in fact, bringing those parts into existence as integral and well-coordinated participants in the meaning of the whole. We heard a fine example of this priority of context over parts in the description of the changing identity of cells within the hair follicle niche.

We hardly need to be told that, in the pages of their professional journals today, biologists constantly mention (although as if merely "in passing") the context-dependence of everything that happens in the organism. The unfortunate fact is that they really do pass such phrases by without making much of an effort to characterize what they mean by "context". So the charge of mysticism, if applied at all, should probably be leveled at the ubiquitous but unclarified use of the term "context" in today's biology.

Nevertheless, the term *can* be used with a perfectly clear awareness of its profound meaning — even if that meaning doesn't sit well with conventional thought today. We will have plenty of occasion in the chapters ahead for further reference to both "contextuality" and "holism", which are very nearly perfect synonyms. In particular, we will deal specifically with the importance of *organizing ideas* for our understanding of biological contexts in Chapter 21, as well as in the section, "The problem of organic form", in Chapter 12.

Notes

1. See, for example, the brief article summaries in Tan 2013.

2. Figure 6.1 credit: From Rompolas, Mesa and Greco 2013.

3. Rompolas et al. 2013. For an updated and more detailed report on this same research, see Xin et al. 2018.

4. Pierre-Simon, marquis de Laplace (1749-1827) was a mathematician and physicist. The reference is to what is often referred to as "Laplace's demon", although Laplace himself did not use the word "demon":

> We ought then to regard the present state of the universe as the effect of its anterior state and the cause of the one which is to follow. Given for one instant an intelligence which could comprehend all the forces by which nature is animated and the respective situation of the beings who compose it — an intelligence sufficiently vast to submit these data to analysis — it would embrace in the same formula the movements of the greatest bodies of the universe and those of the lightest atom; for it, nothing would be uncertain and the future, as the past, would be present to its eyes … The curve described by a single molecule in air or vapour is regulated in a manner just as certain as the planetary orbits; the only difference between them is that which comes from our ignorance. (Laplace 1951, p. 4)

5. Doing a quick hyperbole-check on myself, I find that a google scholar search on

> "context dependent" gene cell

yields over 200,000 results. (I included the terms "gene" and "cell" in the search in order to insure that the results were mostly from biological texts, with an emphasis on molecular biology.) It would be a worthwhile exercise for the reader to execute that search (by clicking here) and then browse down through some of the article titles and excerpts. Or go to scholar.google.com and type in the search terms.

6. It is worth mentioning here that inanimate phenomena are surely contextual as well, even if they lack those focal, organic centers of need and interest that can *respond* to context. The physicist Georg Maier once pointed this out by mentioning that the warm air in a closed room collects near the ceiling, while the air in the earth's atmosphere generally becomes cooler with elevation.

Of course, the ideas evident in inanimate phenomena are very different from the ones we find in the phenomena of life. But ideas do remain ideas: we may prefer to formulate the regularities in physical events as high, mathematical abstractions, but they are ideas nonetheless. The seemingly willful blindness to this obvious fact may be the central pathology of contemporary science.

Sources

Albrecht-Buehler, Guenter (1985). “Is Cytoplasm Intelligent Too?”, Chapter 1 in *Cell and Muscle Motility*, edited by Jerry W. Shay, pp. 1-21. Boston: Springer.

Arber, Agnes (1985). *The Mind and the Eye: A Study of the Biologist’s Standpoint*, with an introduction by P. R. Bell. Cambridge: Cambridge University Press. Originally published in 1954.

Goldstein, Kurt (1995). *The Organism: A Holistic Approach to Biology Derived from Pathological Data in Man*, with a foreword by Oliver Sacks. New York: Zone Books. Originally published in German in 1934, and in English in 1939.

Haldane, J. S. (1931). *The Philosophical Basis of Biology*. Donnellan Lectures, University of Dublin, 1930. Garden City NY: Doubleday, Doran & Company.

de Laplace, Pierre Simon, Marquis (1951). *A Philosophical Essay on Probabilities*, translated from the sixth French edition by Frederick Wilson Truscott and Frederick Lincoln Emory with an introductory note by E. T. Bell. New York: Dover. Originally published in 1814.

Lewontin, Richard C. (1983). “The Corpse in the Elevator”, *New York Review of Books* vol. 29, nos. 21-22 (January 20), pp. 34-37. https://www.nybooks.com/articles/1983/01/20/the-corpse-in-the-elevator/

Rompolas, Panteleimon, Kailin R. Mesa and Valentina Greco (2013). “Spatial Organization within a Niche as a Determinant of Stem-Cell Fate”, *Nature* vol. 502 (October 24), pp. 513-18. doi:10.1038/nature12602

Russell, E. S. (1930). *The Interpretation of Development and Heredity: A Study in Biological Method*. Reprinted in 1972. Freeport NY: Books for Libraries Press.

Russell, E. S. (1945). *The Directiveness of Organic Activities*. Cambridge UK: Cambridge University Press.

Tan, Jiaying (2013). “Stemness in the Niche”, *Cell* vol. 155 (December 19), pp. 1439-40. doi:10.1016/j.cell.2013.12.003

Tata, Purushothama Rao, Hongmei Mou, Ana Pardo-Saganta et al. (2013). “Dedifferentiation of Committed Epithelial Cells into Stem Cells *in Vivo*”, *Nature* vol. 503 (November 14), pp. 218-23. doi:10.1038/nature12777

Thompson, D’Arcy Wentworth (1917). *On Growth and Form*. Cambridge: Cambridge University Press. Available at https://www.gutenberg.org/ebooks/55264

Weiss, Paul (1962). “From Cell to Molecule”, in *The Molecular Control of Cellular Activity*, edited by John M. Allen, pp. 1-72. The University of Michigan Institute of Science and Technology Series. New York: McGraw-Hill.

Weiss, Paul A. (1970). “The Living System: Determinism Stratified”, in *Beyond Reductionism: New Perspectives in the Life Sciences*, edited by Arthur Koestler and John R. Smythies. New York: Macmillan, pp. 3-42. Reprinted in Weiss 1971, pp. 262-311.

Weiss, Paul A. (1971). *Within the Gates of Science and Beyond: Science in Its Cultural Commitments*. New York: Hafner.

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

Xin, Tianchi, David Gonzalez, Panteleimon Rompolas and Valentina Greco (2018). “Flexible Fate Determination Ensures Robust Differentiation in the Hair Follicle”, *Nature Cell Biology* vol. 20 (December 1), pp. 1361-69. doi.org/10.1038/s41556-018-0232-y

CHAPTER 7

Epigenetics: A Brief Introduction

You and I harbor trillions of "sub-creatures" in our bodies. I am not referring to the microorganisms in our guts, but rather the cells we consider our own — the constituents of our muscles and brains, our livers and bones, our lenses and retinas. Each of these cells, embedded in its supportive environment, sustains a dauntingly complex and unique way of life. If we had first discovered such cells floating singly in a pool of water and had observed them through a microscope, we would have judged them to be distantly related organisms. Phenotypically (that is, in visible form and function) one cell type can differ from another as much as an amoeba differs from a paramecium.

All the cells in the human body have descended from a single cell (zygote) with a single genome.[1] And just as hundreds of different cell types have arisen from that one zygote, so, too, have the multicellular, intricately organized entities we know as lung, heart, eye, kidney, and pancreas, along with all our other organs. Supremely interdependent as these are, each is nevertheless a functioning organic world of altogether distinctive character.

For the past century these facts of development have been thought to present a (largely ignored) problem for the gene-centered view of life. The developmental biologist Frank Lillie, who had directed the prestigious Marine Biological Laboratory at Woods Hole, Massachusetts, and would go on to become president of the National Academy of Sciences, remarked in 1927 on the contrast between "genes which remain the same throughout the life history" of an organism, and a developmental process that "never stands still from germ to old age". In his view, "those who desire to make genetics the basis of physiology of development will have to explain how an unchanging complex can direct the course of an ordered developmental stream" (Lillie 1927, pp. 367-68).

This ordered developmental stream, of course, includes generation of the hundreds of different cell types in our bodies. It is hard to understand how a single genomic "blueprint" — or any other way of construing a fixed genetic sequence — could by itself provide the definitive causal basis for these hundreds of radically distinct ways of living. If the blueprint is compatible with all of them, do we have compelling grounds for thinking that it fundamentally *determines* any one type of cell, or organ, let alone all of them together? One might reasonably expect that other factors direct the developmental process toward particular outcomes of such different sorts.

A more balanced understanding arises when we watch how every cell displays its character through its life as a whole. That character, in all its qualitative richness, somehow seems decisive. DNA is *caught up in* a seamless and integral way of being. When we grasp this integral nature, we quickly realize that the idea of DNA as the crucial causal determinant of the whole is an impossible one. As a specific kind of liver cell passes through its developmental lineage, it must sustain its entire organization in a coherent and well-directed manner from one cell generation to the next — including, for example, the cytoskeletal and cell membrane organization described in Chapter 4. It must also bring about and orchestrate the elaborate performances of its chromosomes we saw in Chapter 3 — performances that are unique to each type of cell and that chromosomes themselves have no way to set in motion.

(We will look at this "ordered developmental stream" from a slightly difficult angle — and in an evolutionary context — in Chapter 17.)

Every individual part, including DNA, is shaped by, and gives expression to, the character of a larger whole. Only when we recognize that genes participate in a living whole can we find an answer to Lillie's challenge "to explain how an unchanging complex can direct the course of an ordered developmental stream". The answer — so we will find — is that there is no unchanging complex. Genes, like all parts of a cell or organism, gain their identities and meanings only within the context of innumerable, interpenetrating, living narratives expressing diverse physiological characters.

An old problem newly recognized

Passing from Lillie's day to our own, we find a peculiarly late-arriving acknowledgment of old problems. Here is where we encounter that rather mysterious and too often abused keyword of contemporary molecular biology: *epigenetics* (along with its companion, *epigenome*). The discipline of epigenetics drives today's effort to come to terms with the relationship between genes and the organisms that put those genes to such diverse uses.

But today the question has gained additional dimensions. The Human Genome Project and its successors surprised many by revealing an unexpectedly low number of human genes relative to many other organisms — roughly the same number, for example, as in the simple, one-millimeter-long, transparent roundworm, *Caenorhabditis elegans*. Many began to ask: If genes really do account for the organism in all its complexity, how can it be that a primitive worm boasts as many genes as we do? "As far as protein-coding genes are concerned", wrote Ulrich Technau, a developmental biologist from the University of Vienna, "the repertoire of a sea anemone … is almost as complex as that of a human" (Technau 2008, p. 1184).

A further revelation only compounded the difficulty: our own genome was found to have a great deal in common with that of many animals. In particular, we were said to share about 98.5% of our genome with chimpanzees. A good deal of verbal hand-wringing and chest-beating ensued. How could we hold our heads up with high-browed, post-simian dignity when, as the *New Scientist* reported in 2003, "chimps are human"? If the DNA of the two species is more or less the same, and if, as nearly everyone seemed to believe, DNA is destiny, what remained to make us special? Such was the fretting on the human side, anyway. To be truthful, the chimps didn't seem much interested.

All this news conspired to bring epigenetics to the fore. In 2010 the editors of the journal *Nature* wrote:

> By 2004, large-scale genome projects were already indicating that genome sequences, within and across species, were too similar to be able to explain the diversity of life. It was instead clear that epigenetics … could explain much about how these similar genetic codes

> are expressed uniquely in different cells, in different environmental conditions and at different times (Nature editors 2010).

And in 2015 a contributor to the same journal described a huge, epigenome-centered project, sponsored by the US National Institutes of Health, which was "likely to provide a leap forward in pinning down one of the central mysteries of biology: how do cells with the same genetic instructions take on wildly different identities?" (Ledford 2015). Lillie's old question had finally come center stage. But had the meaning of the question really been recognized? And what, after all, *is* this mysterious thing called *epigenetics*?

Epigenetics — a useful term?

Etymologically, the word *epigenetics* suggests something like "on top of genetics" or "added to genetics". In common technical use, the word refers today to "heritable changes in gene function that are not due to changes in DNA sequence" — where the *DNA sequence* is a succession of nucleotide bases constituting the "letters" of the so-called genetic code, and *heritable* applies not only to what can pass from parent organisms to their progeny, but also what passes from any given cell to its daughter cells. In other words, *epigenetic* refers to that which is not rock-bottom genetics — not genetics proper (which conventionally centers on the DNA sequence alone) — while yet somehow bearing on *functional* genetics, both within organisms and between generations.

The common usage, however, remains deceptively gene-centered. This is shown by the prevailing notion that epigenetics has to do only with secondary "annotations" of the primary "genetic program". For example, researchers, having discovered certain chemical transformations of both DNA and the overall substance of chromosomes, typically refer to these transformations as innocent-sounding and transient "marks" on an otherwise fundamental and essentially unchanging entity. In this way all those aspects of the cell's management of its DNA we looked at in Chapter 3 tend to be overlooked or trivialized.

It is hard to avoid the suspicion that biologists refer to the chemical transformations as mere marks only because they have concluded up front that whatever cells do with their genome cannot be considered genuinely transformative and creative — cannot redefine what a gene is. They prefer to keep the genome a kind of static, "eternal" essence (Chapter 22) that, unlike every other part of an organism, need not continually *become* what it is or else cease to live.

Rather than think of epigenetics as the application of incidental marks, we could conceive it more realistically as encompassing all the ways DNA is caught up in the activity of its larger context and brought into service of the whole. I say "more realistically" because there is, in fact — as two molecular biologists have phrased it in the journal *Nature* — "an avalanche of biochemical evidence revealing a complex and versatile array of molecular mechanisms that regulate gene expression without changing DNA sequences" (Cervantes and Sassone-Corsi 2019).

In other words, what genes mean to the organism is not merely a matter of the DNA sequence or a "genetic code". It is more a question of the many different ways an organism can employ its genes.

So the word *epigenetics* may usefully remind us that what is "on top of" DNA is nothing less than the functioning organism as a whole. But a word that threatens to encompass just about everything begins to lose its value as a special term. And this in turn suggests that we could just as well retire the word "epigenetics" and get on with describing how organisms carry out their organically integrated lives — express their own character — in part by constraining their genes to serve that character.

Unexpected Discoveries

In the mammalian genome, chromosomes normally come in pairs, one inherited from the mother and the other from the father. Any given gene occurs twice, with separate versions (*alleles*) located on the two chromosomes. These two alleles may or may not be identical. For example, there are mice that, in their natural (*wildtype*) state are dark-colored — a color that is partly dependent on a gene known as *Kit*. The mice normally have two identical copies of this gene. When, however, one of the *Kit* alleles is mutated in the laboratory a certain way, the mouse shows white feet and a white tail tip.

That result was perfectly natural (if you call such artificial gene manipulations "natural"). But it is also where the story becomes interesting. Scientists at the University of Nice-Sophia Antipolis in France took some of the mutant, white-spotted mice and bred them together (Rassoulzadegan et al. 2006). In the normal course of things, some of the offspring were again wildtype animals — neither of their *Kit* alleles was mutant.

However, to the researchers' surprise, these "normal", wildtype offspring maintained, to a variable extent, the same white spots characteristic of the mutants. It was an apparent violation of Mendel's laws of inheritance: while the genes themselves were passed between generations properly, their effects did not follow the "rules". A trait was displayed despite the absence of the gene previously corresponding to it. Apparently something in addition to the genes themselves — something "epigenetic" — figured in the inheritance of the mice offspring, producing the distinctive coloration.

Another group of researchers, led by Michael Skinner at the University of Washington, looked at the effects of the fungicide vinclozolin on laboratory rats. (Anway et al. 2006; Crews et al. 2007). Banned in Scandinavia and Europe but allowed on some crops in the U.S., vinclozolin is an endocrine-disrupting chemical. If pregnant female rats are exposed to it while their embryos are undergoing sexual organ differentiation, the male offspring develop serious problems as adults — death of sperm-generating cells, lowered sperm count and motility and, later, immune abnormalities and various diseases including cancer. The remarkable thing is that the effects were found to be transmitted over four generations without weakening. That is, acquired characteristics — deficiencies in embryos brought on by fungicide exposure — were inherited by offspring who were not subject to the same exposure.

Inheritance aside, puzzling results such as these put the question, “Are genes equivalent to destiny?” in a new light. In 2007 a team of researchers at Duke University reported that exposure of pregnant mice to bisphenol A (a chemical that was then used in many common plastics such as baby bottles and dental composites) “is associated [in the offspring] with higher body weight, increased breast and prostate cancer, and altered reproductive function”. The exposure also shifted the coat color of the mice toward yellow — a change again found to be transmitted across generations despite its not being linked to a gene mutation. Moreover, the changes brought on by the chemical were negated when the researchers supplemented the maternal diet with folic acid, a B vitamin (Dolinoy et al. 2007).

And so an epigenome that responds to the environment can respond to healthy as well as unhealthy influences. As another early illustration of this: researchers at McGill University in Montreal looked at the consequences of two kinds of maternal behavior in rats. Some mother rats patiently lick and groom their newborns, while others generally neglect their pups. The difference turns out to be reflected in the lives of the offspring: those who are licked grow up (by the usual measures) to be relatively confident and content, whereas the neglected ones show depression-like symptoms and tend to be fearful when placed in new situations.

This difference is correlated with different levels of activity in particular genes in the hippocampus of the rats’ brains. Not that the gene sequences are themselves mutated in the usual sense. Rather, the researchers found that various epigenetic modifications in the hippocampus alter the way the genes work (Weaver et al. 2004). Other investigations have pointed toward similar changes in the brains of human suicide victims who were abused as children (Poulter et al. 2009).

What has perhaps excited the general public most is this application of epigenetic studies to human beings. Take, for example, the frequently cited Dutch Hunger Winter during the winter and spring of 1944-45. The much-studied effects of this famine were found to extend, not only to the children of women who were pregnant during the months of hunger, but also to their grandchildren.

Such findings seemed to suggest that our environments and our responses to those environments can play a major, heritable role in shaping our lives. This seems to have encouraged in many the hopeful thought, “Maybe we are not really just gene-driven machines” — which surely is true enough, but also rather strange. I will try to explain.

Grasping at epigenetic straws — is it really necessary?

Those early discoveries in epigenetics — especially when treated more expansively and brought more up-to-date (Chapter 14) — are truly profound and far-reaching in their implications. But they are profound only in the way everything about the character of organic life we have been discussing in the preceding chapters is profound.

Genes as self-sufficient or definitive First Causes simply don’t exist. They never did have a reasonable place in our conceptualization of living beings — something that early twentieth-century critics of gene theory clearly saw (Russell 1930). Every organic process, including every genetic process, is an expression of the life of the whole cell and whole organism. In other words, the only genetics we have is epigenetics.

All this is to say that the crucial thing, if we want to transcend the notion of organisms (or ourselves) as gene-driven machines, is to rise above the entire, spirit-killing picture of mechanistic, gene-programmed life processes. We need to recognize this picture for the fantasy it really is.

Anyone who doubts the scale of the challenge in this need only look at what began happening quickly after the discovery of “epigenetic” effects. No sooner had certain gene-regulatory “marks” been found on key elements of the chromosome than some began to suggest that they constituted just another “code” — an *epigenetic code* (Strahl and Allis 2000). An epigenetic “program” was said to contain “instructions” for “control of gene expression”. And so an editorial entitled “Time for Epigenetics” in the *International Journal of Biochemistry & Cell Biology* told us that

> The genome and epigenome together *determine* the phenotype and hence, the function and characteristics of a cell at any given point in development and during differentiation. At the core of gene regulation are elaborate *molecular programs* that alter the packaging of DNA into chromatin, thereby regulating DNA accessibility to transcription complexes and providing cues to the activation or repression of *gene regulatory programs* (Altucci and Stunnenberg 2009; emphasis added).

In other words, the attempt is to assimilate epigenetics to the existing understanding of genetic “programs” and “instructions”. The programs and the instructions simply become a little larger and more complex, but the same basic understanding of ourselves as collections of molecular automatons remains.

Or, again, we hear that the epigenome involves a “re-wiring of transcription factor circuits” (Tsankov et al. 2015), as if there were some fixed and standard genetic wiring scheme waiting to be rewired. But — as if biology as a discipline were somehow “of two minds” about such things — the authors of this paper healthily refer to the rewiring as “context-dependent” and “dynamic”. So the terminology appears to be impossibly conflicted. If in fact the governing context is always to some degree fluid, dynamic, and shifting, where do we ever see anything remotely analogous to wires constraining all the relevant molecules to go where they need to go, and to do so in the right time, in the right quantities, and with the right molecular partners?

The picture of a wired cell may sound conveniently causal, but it makes no sense. Biologists are sooner or later going to have to decide which half of their descriptive language they are going to side with. Meanwhile, those of us trying to decipher what "epigenetics" really means can usefully remind ourselves that the deeper issue has to do with the overall terms of the description ultimately decided upon, not with particular "epigenetic" insights that are too easily assimilated to traditional, machine-based understanding.

Nothing is *merely genetic*. Every so-called genetic activity is an expression of its entire context, and therefore is altogether epigenetic. Genetics cannot be abstracted from the rest of the organism. So we can safely say, "All genetics is epigenetics".

WHERE ARE WE NOW?

Bringing Back the Organism

As we move along, we have been seeing more and more how the "molecule's eye view", whatever it may tell us about the physics and chemistry of molecules, tells us little or nothing about biological meaning, for which a wider perspective is required. In the end, the meaning of things depends on what the cell or organism is *doing* in its coordination of countless diverse but interwoven processes. An organism just *is* its unified doings, its consistent way of living in its world.

It is perhaps in the field of genetics that biologists have most stoutly resisted this recognition of integral wholeness and significant context. Genes, conceived as First Causes, must exist in exalted isolation. But because of the intensity of research focused on genetics, it is also in this field that the illusions of strictly physical and chemical explanation of the organism are being most strikingly dispelled — even if geneticists are proving slowest at accepting the fact.

The brief introduction to epigenetics in this chapter will be greatly expanded in Chapter 14, "How Our Genes Come to Expression". There I try at least to suggest the endless web of pathways through which the cell brings about its almost infinitely complex patterns of gene expression.

Then we will deepen this picture by bringing the gene into connection with heredity and evolution in Chapter 20 and Chapter 21. There we will learn how it is that genes rendered the organism invisible to the evolutionist's sight — and how false that substitution of genes for organisms has proven.

Notes

1. This has been the standard statement for a very long time. However, we now know that many people have some cells derived from a different genome. For example, a fetus may assimilate cells from its mother, and there can be an exchange of cells between fraternal twins in the womb, even if they are oppositely gendered. The conventional statement, however, serves well enough for our purposes.

Sources

Altucci, Lucia and Hendrik G. Stunnenberg (2009). “Time for Epigenetics”, *International Journal of Biochemistry & Cell Biology* vol. 41, no. 1, pp. 2-3. doi:10.1016/j.biocel.2008.09.010

Anway, Matthew D., Charles Leathers and Michael K. Skinner (2006). “Endocrine Disruptor Vinclozolin Induced Epigenetic Transgenerational Adult-Onset Disease”, *Endocrinology* vol. 147, no. 12 (December), pp. 5515-23. doi:10.1210/en.2006-0640

Crews, David, Andrea C. Gore, Timothy S. Hsu and Michael K. Skinner (2007). “Transgenerational Epigenetic Imprints on Mate Preference”, *PNAS* vol. 104, no. 14, pp. 5942-46. doi:10.1073/pnas.0610410104

Cervantes, Marlene and Paolo Sassone-Corsi (2019). “Modification of Histone Proteins by Serotonin in the Nucleus”, *Nature* vol. 567 (March 13), pp. 464-65. doi:10.1038/d41586-019-00532-z

Dolinoy, Dana C., Dale Huang and Randy L. Jirtle (2007). “Maternal Nutrient Supplementation Counteracts Bisphenol A-induced DNA Hypomethylation in Early Development”, *PNAS* vol. 104, no. 32 (August 7), pp. 13056-61. doi:10.1073/pnas.0703739104

Ledford, Heidi (2015a). “The Genome Unwrapped”, *Nature* vol. 528 (December 3), pp. S12–S13. doi:10.1038/528S12a

Lillie, Frank R. (1927). “The Gene and the Ontogenetic Process”, *Science* vol. 46, no. 1712 (October 21), pp. 361-68. https://www.jstor.org/stable/1651140

Nature editors (2010). “Time for the Epigenome”, *Nature* vol. 463, no. 7281 (February 4), p. 587. doi:10.1038/463587a

Poulter, M., L. Du, I. Weaver, et al. (2009). "GABAA Receptor Promoter Hypermethylation in Suicide Brain: Implications for the Involvement of Epigenetic Processes", *Biological Psychiatry* vol. 64, no. 8, pp. 645-52. doi:10.1016/j.biopsych.2008.05.028

Rassoulzadegan, Minoo, Valérie Grandjean, Pierre Gounon et al. (2006). “RNA-mediated Non-Mendelian Inheritance of an Epigenetic Change in the Mouse”, *Nature* vol. 441 (May 25), pp. 469-74. doi:10.1038/nature04674

Russell, E. S. (1930). *The Interpretation of Development and Heredity: A Study in Biological Method*. Reprinted in 1972. Freeport NY: Books for Libraries Press.

Strahl, B. D. and C. D. Allis (2000). “The Language of Covalent Histone Modifications”, *Nature* vol. 403, no. 6765 (Jan 6), pp. 41-45. doi:10.1038/47412

Technau, Ulrich (2008). “Small Regulatory RNAs Pitch In”, *Nature* vol. 455 (October 30), pp. 1184-85. doi:/10.1038/4551184a

Tsankov, Alexander M., Hongcang Gu, Veronika Akopian et al. (2015). *Nature* vol. 518 (February 19), pp. 344-49. doi:10.1038/nature14233

Weaver, Ian C. G., Nadia Cervoni, Frances A. Champagne et al. (2004). “Epigenetic Programming by Maternal Behavior”, *Nature Neuroscience* vol. 7, no. 8 (August), pp. 847-54. doi:10.1038/nn1276

Chapter 8

The Mystery of an Unexpected Coherence

We heard in Chapter 2 that living activity has a certain future-oriented (purposive or directive) character that is missed by causal explanations of the usual physical and chemical sort. The end is always more constant than the continually adjusted means. This is true whether we are talking about a dividing cell, the achievement of adult form through development, or the strategy for taking a prey animal for food (or avoiding being taken).

An animal's end-directed activity may, of course, be very far from what we humans know as conscious aiming at a goal. But all such activity, human or animal, displays certain common features distinguishing it from inanimate proceedings: it tends to be *persistent*, so that it is resumed again and again after being blocked; it likewise tends to be *adaptable*, changing strategy in the face of altered circumstances; and the entire activity *ceases* once the end is achieved.

This flexible directedness — this interwoven play of diverse ends and means within an overall living unity — is what gives the organism's life its peculiar sort of multi-threaded, narrative coherence. Life becomes a story. Events occur, not merely from physical necessity, but because they hold *significance* for an organism whose life is an unfolding pattern of significances.

The idea of narrative coherence, like the related idea of a governing context (Chapter 6), is a mystery for all attempts at purely physical explanation. This is why even the explicit acknowledgment of an organism's *striving for life* — central as it may be for evolutionary theory — is discouraged whenever biologists are describing organisms themselves. It sounds too much as if one were invoking inner, or soul, qualities rather than material causes — acknowledging a *being* rather than a thing. And it is true that our physical laws as such, however combined, nowhere touch the idea of *striving*.

Biologists much prefer to identify discrete, definitive causes. The cell nucleus with its genome has long been viewed as the seat of such causation. But, as we saw in our discussion of DNA (Chapter 3), and epigenetics (Chapter 7), the single-minded pursuit of genetic causes has forcibly redirected our attention to epigenetics, where we have discovered that genes are circumscribed and given their meaning by the directive life of the entire cell and organism.

In what follows below we will consider this directive coherence in a more detailed way by taking up one of the many activities of the cell that are often considered under the heading of "epigenetics". Then we will look at a startling phenomenon that, already on its face, renders absurd the idea of central genetic control. In both cases we will be focused on molecular-level activity, which is precisely where we have been most strictly taught to expect the absence of any coherence other than that of "blind mechanism".

Flexibility and precision in RNA splicing

The discovery of *RNA splicing* in the late 1970s was one of the transforming moments in the history of molecular biology. To put it in informal terms: the cleanly autocratic mastery of DNA gave way to massive presumption by various scruffy elements of the cellular “rabble”. The idea had originally been that a molecule of messenger RNA (mRNA) was produced as a direct image of the “instructions” in a protein-coding gene and was then exported from the cell nucleus to the cytoplasm. There it yielded passively to *translation*, a process whereby a protein was supposedly produced according to the exact specifications of the “genetic code” previously copied from DNA into the mRNA.

Our growing knowledge of RNA splicing has, together with many other developments in molecular biology, exploded just about every aspect of this picture. We now know that, via an elaborately orchestrated improvisational drama, many so-called *epigenetic* elements in the cell (Chapters 7 and 14) come together to help decide what use will be made of any particular gene.

In particular, the cell has innumerable ways to obtain and sculpt its proteins. RNA splicing is just one of these — a massive reconfiguration process whereby a cell decides which portions of an initially produced (*precursor*) RNA to cast aside for other uses, and which ones to “splice” together into a mature mRNA. As we have come to expect by now, these choices are strongly context-dependent, with different protein variants being produced in different kinds of cell or tissue, or under different cellular conditions.

This splicing involves much more than a minor stitch or two. The large human dystrophin gene (whose malfunction is related to some forms of muscular dystrophy) is said to require 16 hours for its transcription from DNA into RNA. Of this time, 15 hours and 54 minutes is required for transcripton of the non-protein-coding RNA sequences that will have to be spliced out of the RNA in order to obtain a mature messenger RNA. That may be a somewhat extreme case, but it remains true that the sequences to be discarded are “commonly orders of magnitude longer” than the remaining portions fit for the synthesis of protein (Papasaikas and Valcárcel 2016).

But the most dramatic transformation involves the sequences remaining after removal of the non-protein-related (“noncoding”) content. The splicing activity can often select from among these sequences in differing ways, thereby determining which functional portions of the precursor molecule will be included in the mature mRNA. The protein eventually resulting will vary depending on these *alternative splicing* decisions. (The protein variations are referred to as *isoforms*.)

Over 90 percent of mammalian genes are thought to be alternatively spliced, contributing greatly to physiological complexity. According to one paper, “As cells differentiate and respond to stimuli in the human body, over one million different proteins are likely to be produced from less than 25,000 genes” (de Almeida and Carmo-Fonseca 2012).

Further, “even relatively modest changes in alternative splicing can have dramatic consequences, including altered cellular responses, cell death, and uncontrolled proliferation that can lead to disease” (Luco and Misteli 2011). The title of one technical paper makes the point vividly: “Cell Death or Survival Promoted by Alternative Isoforms of [the protein] ErbB4”.

The spliceosome

You have doubtless heard many times how a mutation or engineered alteration of such-and-such a gene “causes” this or that result. How often, by contrast, do you hear that a slight change in the way your cells orchestrate the sculpting of this or that protein can make the difference between life and death?

The central player in the splicing drama is known as the *spliceosome*, which is not so much a rigidly fixed thing or structure as it is a complex performance. The performers include a few critically important small RNAs and over 150 proteins.[1] Together — although in several, separate, coordinated groups that must continually reconfigure themselves during the process — they excise the protein-unrelated pieces of the RNA and then stitch together a selection of the ones remaining. Misjudging any of the potentially many places to cut the mRNA — shifting the point of severance by a single “letter”, or nucleotide base, out of (in many cases) thousands — could possibly render the resulting mRNA useless for producing protein, if not downright harmful.

We heard a little bit in Chapter 3 about the puzzle of topoisomerases. In a way that is difficult to fathom, these molecules make cuts in the DNA double helix in order to release knots and “untangle” the seemingly indecipherable spatial complexity of chromosomes (46 in the human case) that are tightly packed into the cell nucleus. But the challenge for the spliceosome as it does its work seems no less daunting. And the fact that there is indeed coherently describable *work* to do already takes us beyond normal physical explanation to the idea of an unfolding meaning.

The key, chemically active part of the spliceosome complex “is short lived and reconstructed from individual pieces for each splicing event” (Papasaikas and Valcárcel 2016). This is the part that actually cuts and stitches together the RNA once the end-points for the next excision are chosen. Moreover, few of the scores of proteins required for the activity stay together throughout the intricate work on a single RNA. “At all transitions in the splicing process, the spliceosome’s underlying RNA-protein interaction network is compositionally and conformationally remodeled and at each step there is a massive exchange of [spliceosomal] proteins” (Wahl and Lührmann 2015).

But there is more. In multicellular organisms the mRNA being remodeled possesses particular sequences that are supposed to act as signposts for “attracting” the elements of the spliceosome to the correct sites for cutting and stitching. But these signposts are often ambiguous or contradictory, and provide only more or less vague hints. This is despite the extraordinary complexity of the task facing the spliceosome, and the large number of segments that commonly require removal.

“It has been proposed”, write two researchers, “that thousands of different sequences” can function as a certain kind of directive for the spliceosome, but these sequences are highly variable, having only a few loci in common. Further, many sequences that look rather like splice sites are ignored by the spliceosome, while other sequences, despite lying at a distance from the splice sites, nevertheless contextually influence site recognition. So it appears that "hundreds of regulatory motifs may need to be integrated" (and understood) in order for the spliceosome to accomplish its surgery in harmony with current cellular needs (Papasaikas and Valcárcel 2016).

Using the thing-oriented (rather than process-oriented) language available to us, it is difficult not to speak of the spliceosome as a fixed structure, and equally difficult to avoid suggesting that it has a specific and well-defined task. What we see, however, is a remarkable plasticity. This is illustrated, for example, by the fact that "nearly all 'activators' of splicing can, in some cases, function as repressors, and nearly all 'repressors' have been shown to function as activators … it is clear that context affects function" (Nilsen and Graveley 2010).

This context-sensitivity extends to the very definitions of the various tasks, which can look utterly different, and require wholly different approaches and capabilities on the part of the spliceosome, depending on the situation. Is the task to skip the next protein-coding segment of the RNA? Is it to make sure that a choice is made between two such segments — to retain only one and remove only one? Is it to choose an alternative location for the beginning or end of a particular segment? Is it, in at least some cases, to make the radical choice of preserving a non-protein-coding segment in the final mRNA?

Each of these operations demands a different sort of coordination among the many molecules involved, and the ways of approaching the work can vary, one might almost say, "wildly". "Mechanisms of alternative splicing are highly variable, and new examples are constantly being found."[2] So there is not just one "spliceosome machine" (as some would like to call it), and not just one task. The numerous molecules participating (or capable of participating, but "electing" not to) in the various splicing operations face the challenge of working together in an unimaginably sophisticated manner that somehow reflects the wider context and the needs of the cell.

Who will disagree with the researchers who write, in what might even be an understatement: "Working in a highly orchestrated manner, [the many parts of the spliceosome] perform incredible feats of molecular gymnastics with each round of splicing" (Chen and Moore 2014)?

And further: everything *could* go backward

The entire problem is perhaps most vividly framed when we consider one further fact about RNA splicing. Not only is the spliceosome "a remarkably dynamic and flexible molecular machine; its transitions are so malleable that the whole reaction can eventually be reversed[3] to generate precursor mRNA from spliced products" (Papasaikas and Valcárcel 2016). More particularly:

> Rather than being the one-way pathway typically drawn in textbooks, almost every step in the spliceosome cycle is readily reversible … [For example, regarding the first and second

> chemical steps in splicing,] not only can the spliceosome catalyze both chemical steps in forward and reverse, it can even convert spliced products … back into unspliced precursor mRNA! (Chen and Moore 2014)

That is, the splicing choreography can take an already spliced RNA along with a section previously removed from it, and *reinsert* that section into the RNA.

The reversibility and flexibility underlying the finely gauged, discriminating, and "perceptive"[4] activity of RNA splicing are hard to overestimate. Plasticity is layered upon plasticity, and complexity upon complexity. For example, many of the individual proteins coming together in continually different ways in the spliceosome are themselves subject to modifications that are often decisive for how they will function within their current context. And these modifications, too, are dynamic and reversible.

They are also mutually entangled, with one kind of modification in one protein likely affecting, or being affected by, diverse modifications in other proteins. The untraceable lines of cause and effect blur into — and become subordinate to — the overall storyline.[5]

Can DNA coordinate splicing activity?

Despite the fact that a specific splicing process could, with perfect *physical* propriety, go in an infinite number of different directions, it produces, from among all the present possibilities, the particular result that fits the ever-changing cellular context at the present moment. Splicing must, in some extremely significant sense, be guided by this context. If it were somehow being "dictated" to by a specific element or group of elements in the cell, those elements would have to have incorporated within themselves an effective sense for the current state of the entire cell. But then, why not just recognize that a biological whole, in one way or another, informs *all* its parts?

It is worth noticing the great distance between, on one hand, what RNA splicing shows us and, on the other hand, the idea of DNA as a decisive cause of the cell's life (or even merely DNA as a strict determinant of protein synthesis). The notion of a decisive physical cause immediately comes up against questions such as the following:

> Does DNA single-handedly "dictate" that the splicing operation on a particular RNA *this time* should differ in such-and-such a way from how it was done *last time*?
>
> Does DNA (or, for that matter, any other cellular feature) have any possibility of determining the specific and crucial, well-timed chemical modifications or changes in form of just one of the proteins involved in the splicing activity, let alone the mutually interacting modifications that must occur in a great number of them as the splicing "surgery" proceeds?
>
> Does DNA enforce the way these proteins (and other molecules) come together in distinct configurations at one point in the process, or dissociate at other points, or come together in a new configuration at yet another point — all in the temporal order required for the success of the overall procedure?
>
> In sum, are there computer-like lines of communication through which coordinating *instructions* can be conveyed from DNA to the individual protein and RNA molecules?

And what we have said about DNA and splicing can also be said about DNA and just about any of the innumerable other molecular processes of the cell, from metabolism, to energy management, to establishment and management of the diverse structural features of the cell, to gene expression, to cell division and much more. Further, all the complexities of each of these spheres of activity must be harmonized with those of the other spheres so as to yield the overall integral unity of cell, organ, and organism — this in the face of the fact that many molecular players are common to the different processes.

Shattering the Genome

Our second case is a long way from RNA splicing — and also, it might seem at first, from the human being.

A dose of ionizing radiation equal to 10 grays (a measure of absorbed radiation) is lethal to the human body. Most bacteria cannot survive 200 grays. But then there is the bacterium known as *Deinococcus radiodurans*: it can endure over 17,000 grays and do quite well, thank you. Never mind that its genome is thoroughly shattered by the assault.

Here's what happens. Ionizing radiation can damage DNA in various ways, perhaps worst of all by causing double-strand breaks. These are breaks across both strands of the double helix. The familiar bacterium, *E. coli*, not at all untypically, dies when it suffers about four double-strand breaks per each of its four-to-eight circular DNA molecules. *Deinococcus radiodurans*, by contrast, can survive over a thousand double-strand breaks. This means that it continues life after its genome is broken into many hundreds of small fragments. It does so by proceeding to put its genome back together again when living conditions improve — a daunting task, to say the least.

Deinococcus radiodurans is one of a small class of single-celled organisms with extreme radiation tolerance. Actually, it tolerates various other extreme conditions as well — some of which, such as dessication, likewise reduce its DNA to genomic shards. It can, for example, survive in a waterless desert for years until moistened again — which could happen, for example, when winds lift it in a cloud of dust from the Sahara, high into the atmosphere (where it is exposed to damaging ultraviolet radiation 100 to 1000 times that on earth's surface), and across the Atlantic ocean to the South American jungles. *D. radiodurans* can be found on Antarctic ice, on dry frozen marble, and in the farthest depths of the sea.

Who's on first — genes or proteins (or neither)?

Biologists have been intrigued by this peculiar survivor (along with some of its kin) for several decades, and of late they have clarified its story considerably. A central feature of that story is striking, because it points toward a truth about organisms in general, not merely those with extreme survival capabilities. The key finding is this: damage to DNA is not, in the most direct sense, what proves lethal about radiation. The primary issue, instead, is damage to proteins. As long as its proteins remain functional, a cell can reassemble even a badly fractured genome; but with damaged proteins, a cell is done for, with or without an intact genome.

D. radiodurans employs a number of strategies for preserving its rather commonplace "proteome", or total inventory of proteins. These strategies include (1) preventing the oxidative damage that results from radiation, a goal it achieves in good part by means of an especially rich supply of antioxidants; (2) eliminating, before they can cause mischief, any proteins that do get damaged, while recycling their constituents; (3) scavenging amino acids and peptides (protein constituents) from the local environment, a capability that, together with the recycling, supports (4) newly synthesizing any proteins that need replenishing.

The proteome thus preserved is then able to go about the task of reconstructing a shattered genome — a task whose complexity at the molecular level is stunning. (Many a bright but befuddled graduate student has twisted his imagination into knots while trying to picture the various textbook processes of DNA damage repair in human cells.) Nevertheless, the task is accomplished in the cells of all organisms. What distinguishes *D. radiodurans* is its ability to carry out this task to an exceptional degree by maintaining its store of proteins intact under extreme duress.

In sum, according to Anita Krisko and Miroslav Radman, researchers at the Mediterranean Institute for Life Sciences who have been studying *D. radiodurans*, "biological responses to genomic insults depend primarily on the integrity of the proteome … This conclusion is the consequence of the fact that dedicated proteins repair DNA, and not vice versa". Moreover, "this paradigm is fundamental in its obviousness (no living cell can function correctly with an oxidized proteome) and, if it is true, must be universal, that is, hold also for human cells".

All this says something powerful about the longstanding genocentric (gene-centered) bias of biologists. Krisko and Radman delicately hint at the issue when they write in their paper:

> The science of molecular biology was dominated by the notion of information, its storage, transmission, and evolution as encrypted in the nucleotide sequence of nucleic acids [that is, DNA and RNA sequences]. But the biological information is relevant to life only to the extent of its translation into useful biological functions performed, directly or indirectly, by proteins (Krisko and Radman 2013).

This truth, as they also point out, applies to our understanding of cancer and its treatment, which have long been focused on DNA abnormalities. But instead, "an effective cancer therapy by tumor cell killing should target the proteome, or both the proteome and genome, rather than the genome alone". Which is almost to say: it should reckon with the coherent living character of the organism as a whole.

A sense of the whole

It was always a strange thing when biologists, attempting to penetrate the thickly matted tapestry of cellular activity at one or another point and disentangle the threads for analysis, decided that one type of element — the gene or DNA sequence — was the place where all the activity logically begins and from where it is controlled. There is in fact no starting place and no part acting as controller. Any attempt to think in such terms immediately crashes against the facts of cellular behavior. *Deinococcus radiodurans* no more shows proteins to be singularly “controlling” elements than it does DNA.

The work on *D. radiodurans* can remind us that the activity of an organism always reflects something like an immanent “sense of the whole”. Surely the protein molecules in this bacterium do not “know” what their “goal” should be in dealing with all those disordered snippets of DNA. But if the overall living context (Chapter 6) remains sufficiently intact, then the mysterious power of self-realization that we have been gently stalking in these several chapters — the power sustaining the coherent storyline of a life — continues to assert itself. The narrative, whatever its unexpected twists and turns, remains unbroken. If parts can be more fully constituted from their shattered fragments, it is because a functioning whole, with its intelligence, was already there.

The information we conceive as *statically* encoded in DNA is a kind of bland abstraction from the living intelligence at work in cellular *processes*. When we occupy ourselves one-sidedly with genocentric information, it is (to employ a rough analogy) as if we elevated a notebook containing selected words, phrases, definitions, and grammatical guidelines to a pinnacle high above *Moby Dick* or *Faust* or *War and Peace*, worshipping the former as “information” while ignoring the informed and meaningful *activity* through which inert words and phrases are woven into soul-stirring tales.

A phrase-book or dictionary can be an essential resource, but it is the organism (*Deinococcus radiodurans* in the case we have been considering) that uses the dictionary to weave its own story — and even reconstructs the dictionary when the pages fall into a disorganized heap on the floor.

Is an unexpected coherence the problem or the solution?

The problem of what it actually *means* to say, “Molecules accomplish the work of splicing and DNA reconstruction” presents us with one of those vast blanks in scientific understanding that are easily papered over today with informational generalities and convenient pictures of tiny machines busily, and in a “mechanistically” respectable fashion, carrying on the work of a cellular factory.

We already heard about the essential problem from cell biologist Paul Weiss (Chapter 6), who spoke about the many degrees of freedom possessed by the cell’s constituents in their watery medium, and about how these degrees of freedom are so remarkably constrained and disciplined toward the expression of biological order at higher levels of observation. The University of Massachusetts geneticist, Job Dekker, was apparently nodding toward the same problem when he asked: “How do cells ensure that genes only respond to the right regulatory elements while ignoring the hundreds of thousands of others?” (Dekker 2013).

It’s a good and obvious question. An editor of *Science* amplified it this way: “If you think air traffic controllers have a tough job guiding planes into major airports or across a crowded continental airspace, consider the challenge facing a human cell trying to position its proteins”. A given cell, he noted, may make more than 10,000 different proteins under any particular set of conditions, and it typically contains more than a billion individual protein molecules at any one time. “Somehow, a cell must get all its proteins to their correct destinations — and equally important, keep these molecules out of the wrong places” (Travis 2011).

And once more: after a study showed that 70 percent of mRNAs in a cell are specifically localized, Robert Singer of Albert Einstein College of Medicine in New York City called it a “staggeringly large number”. He went on: “It’s almost as if every mRNA coming out of the nucleus knows where it’s going” (quoted in Travis 2011).

Dekker, after posing the problem of a nucleus crowded with regulatory factors, immediately went on to offer what he thought was at least part of the answer:

> Recent work has revealed a surprisingly simple strategy for matching genes to only some regulatory elements, which involves the spatial organization and folding of chromosomes inside the nucleus.

Certainly this folding, which we encountered in Chapter 3, is an important aspect of the cell’s performance. But this doesn’t resolve the problem Dekker started with. To explain the achievement of crucial regulatory connections in the nucleus by citing chromosomal foldings that bring genetic loci and regulatory molecules together in just the right way is merely to reframe the problem in slightly different terms. We still face the same kind of question with which we began: How are the foldings achieved with such evident wisdom? (On the general principle here, see Chapter 11.)

It would help if we could get clear about the fact that there are two profound, and profoundly different, descriptive challenges posed by a cell’s impressively coherent activities. One has to do with the underlying physical and chemical processes. The other concerns the coordination of those processes as an expression of the organism’s needs and interests, intentions and meanings — its whole way of being. Severe confusions arise when we say that science must concern itself only with the first challenge, while assuming that the second one, if it can even legitimately be named, is automatically taken care of by our answer to the first.

Biologists, in their own fashion, do notice the second question. They notice it, as I have repeatedly mentioned, in their putting of questions to themselves (“How does the cell do X?”). They notice it in their acknowledgment that organisms *behave* and undertake *tasks*, something solar systems and lake-bottom sediments never do. And they notice it when they grant that every organism acts *as if* it were a purposive being, even if they immediately feel compelled to explain away this purposiveness by appealing to natural selection (Chapters 2 and 18). What is not so often noticed is the fact that an organism’s purposive way of being and its pursuit of its own interests require a distinctive manner of understanding that *cannot be assimilated to our understanding of inanimate objects*.

Is the entire matter really so vexing? The mystery of the unexpected coherence that molecular biologists confront, for example, in RNA splicing and DNA damage repair is, from a perfectly reasonable point of view, neither a mystery nor unexpected. The problem arises only at the moment when we unreasonably demand that an organism's living performances be explained in an inanimate manner. Then, and only then, do we find we can't make sense of things.

But researchers never can wholly resist the urge to make sense of things. They seek an understanding of whatever issue they are working on by looking for the *coherence* and *meaning* of events. This is necessary in order to provide at least some minimal context for their physical analyses. And it is so natural that it easily occurs without any conscious effort. What then happens, and what so badly distorts the practice of biology, is that this recognized coherence and meaning must be forced into an explanatory mode based solely on physics and chemistry. The result is rarely pretty.

Listen to how Dekker concludes his reflections about the puzzle of genes and the "hundreds of thousands" of regulatory elements they may or may not interact with: "Future studies will no doubt unveil how [certain chromosome domains] are established and how they insulate genes from the wrong crowd."

There you see the uncomfortable conflation of the two different explanatory challenges: those of physics and chemistry on one hand, and those of living activity on the other. In appealing to future studies Dekker is not expressing a hope that they will go beyond the elucidation of physical lawfulness. Yet he speaks as though he were unaware that such lawfulness knows nothing about the "wrongness" of a molecular crowd and therefore cannot explain, or "unveil", how events are so coordinated as to insulate genes from that crowd.

Such efforts at reductionism — efforts to reduce biological meaning to the terms of physical lawfulness — never make any progress. Yes, we dramatically extend our tracing of physical lawfulness in the cell. But, for all the flood of physical data today, the needs, interests, tasks, intentions, and meanings of the organism never become less salient in structuring our understanding. The well-coordinated pattern of chromosome folding is no less a "mystery" than the well-coordinated pattern of gene associations the folding is supposed to explain. After these last several decades of aggressive molecular biological reductionism, we ought at last to admit its failure to ourselves.

The cell biologist, Paul Weiss (Chapter 6), in addressing the larger coherence of the "heaving and churning" cell, did not merely stare, transfixed, at the problem of order within "chaos". He tried to formulate its essence as clearly as possible, often resorting to statements such as this: "The resultant behavior of the population [of cellular constituents] as a whole is infinitely less variant from moment to moment than are the momentary activities of its parts." And so "the system *as a whole* preserves its character" (Weiss 1962, p. 6). And again: When we examine the form and physiology of an organism, we see how "certain definite rules of order apply to the dynamics of the *whole* system … reflected [for example] in the orderliness of the overall architectural design, which cannot be explained in terms of any underlying orderliness of the constituents" (Weiss 1971, p. 286).

What was the *constraining* power through which all those molecules, possessing all those degrees of freedom at their own level, yielded to a consistent order at a higher level — a *physically* unexpected coherence? This was the question Weiss' life-long observation of living cells continually brought him up against. But he was too honest to frame an answer in terms of the science of his day. His virtue lay in nevertheless not shrinking from the problem. He spent a long career investigating and describing the physically lawful performances of cells, but he did not pretend that, in doing this, he was *explaining* the order he observed.

I suspect that, with continuing observation and faithful description (some of which, as I keep remarking, biologists have been doing all along) the "problem" of order and wisdom (thought-fullness) in cells will more and more fade into nothingness.

It is indeed only the effort at reductionism that creates the problem. Cease that effort, and all we have left is the routine scientific task of accurate conceptualization and description. Physicists, after arriving at concepts of law, force, field, and all the rest, do not often complain, "Those are not material *things*; how can we possibly deal with them?" They simply continue investigating, describing, and thinking until an overall, coherent picture is formed. That is what *making sense* of the world means.

It would be strange if the discovery of order in the cell persisted as a *problem*; another name for the discovery of order is, after all, "science". I suppose that the *unexpectedness* of order has been part of the scientist's experience all along. But when we live with it long enough, the unexpected becomes expected. In the end, it simply further strengthens our inalienable sense that we live in a world of coherent meaning.

But this happy ending will not be fully realized in biology until we acknowledge that there are many different ways phenomena can add up to a coherent picture in this cosmos of ours. A sloth is not a lion (Holdrege 2021), ice is not water vapor, and an animal is not a rock. Forcing one sort of coherence into the mold of another by violence is never the answer.

WHERE ARE WE NOW?

The organism’s coherence need not be mysterious

We have arrived at a simple truth: the biologist’s sense of mystery (or “mysticism”) when confronted with the intentional, purposive, and meaningfully expressive aspects of an organism’s life typically arises from the unshakable conviction that there needs to be a purely physical explanation of these aspects. As an *insistence*, this is mere dogma. The requirement of science is that we open-mindedly describe every aspect of every phenomenon in its own terms. It does not require a lot of reflection to see, for example, that organic processes of development and self-realization do not have strictly physical descriptions. Inanimate objects do not persistently and directively engage in efforts to develop and realize themselves.

But this does not mean we are headed toward some kind of mystical conception of the organism. As we will see increasingly in coming chapters, the different aspects of the organism (including the more-than-physical — ideal or archetypal — aspects) require only what all science requires: description in terms that are faithful to the phenomena themselves. To describe the marvelous living coherence of molecular processes in an organism’s cells is no more mystical than to describe the very different but just as marvelous coherence of the laws of physics. It merely requires a willingness to embrace what we see, rather than recoil from it.

What I have said in this chapter will raise the question for many readers, “Is merely describing what we see in its own apparent terms an adequate foundation for science?” The question will be appproached in Chapter 11 (“Why We Cannot Explain the Form of Organisms”) and addressed more fully in Chapter 12 (“Is a Qualitative Biology Possible?”). An even more fundamental question has to do with the role of thought both in our descriptions of the world and in the world itself. Is the refusal to accept thinking and thought as natural aspects of the world the deepest root of the biologist’s unwillingness to take organisms at face value? I will take this up in Chapters 13 and 24.

Notes

1. Estimates of the number of proteins participating in the spliceosome vary widely. Some have said there are more than 300, and others “only” 80 — a good indication of a fluidity of structure that is hard to nail down.

2. Wikipedia article, “Alternative Splicing”, accessed May 11, 2019.

3. Chemical reactions are in general reversible. But the point here is that these particular reactions of the spliceosome occur under conditions where they are *readily* reversible.

4. Obviously, I am not referring to our own conscious perceptive capacities. But neither am I referring to something *less* effective in its own way than our power of perception. Whatever brings the biologically coherent and needful results out of the currently inconceivable, creative "chaos" of the cellular plasm is far beyond our efforts to follow, let alone to reproduce. We have to think of a capacity *higher* than anything we consciously possess, even if — as the psychosomatic unity of the organism suggests — our consciousness is somehow contiguous with this higher capacity.

5. There are many other aspects of RNA splicing not considered here — for example, the role played by certain metal ions in the shift between different spliceosomal protein conformations (and therefore between different protein functioning). Such ions are a long way from the macromolecules in which biologists normally invest their sense of cellular information, and yet their well-informed role is crucial to cellular activity.

Sources

Chen, Weijun and Melissa J. Moore (2014). "The Spliceosome: Disorder and Dynamics Defined", *Current Opinion in Structural Biology* vol. 24, pp. 141-49. doi:10.1016/j.sbi.2014.01.009

de Almeida, Sérgio F. and Maria Carmo-Fonseca (2012). "Design Principles of Interconnections between Chromatin and pre-mRNA Splicing", *Trends in Biochemical Sciences* vol. 37, no 6 (June), pp. 248–53. doi:10.1016/j.tibs.2012.02.002

Dekker, Job, Joanna Wysocka, Iain Mattaj et al. (2013a). "Nuclear Biology: What's Been Most Surprising?", *Cell* vol. 152 (March 14), pp. 1207-8. doi.org/10.1016/j.cell.2013.02.041

Holdrege, Craig (2021). *Seeing the Animal Whole — And Why It Matters*. Great Barrington MA: Lindisfarne.

Krisko, Anita and Miroslav Radman (2013a). "Biology of Extreme Radiation Resistance: The Way of *Deinococcus radiodurans*", *Cold Spring Harbor Perspectives in Biology* doi:10.1101/cshperspect.a012765

Luco, Reini F. and Tom Misteli (2011). "More Than a Splicing Code: Integrating the Role of RNA, Chromatin and Non-coding RNA in Alternative Splicing Regulation", *Current Opinion in Genetics and Development* vol. 21, pp. 366-72. doi:10.1016/j.gde.2011.03.004

Nilsen, Timothy W. and Brenton R. Graveley (2010). "Expansion of the Eukaryotic Proteome by Alternative Splicing", *Nature* vol. 463 (January 28), pp. 457-63. doi:10.1038/nature08909

Papasaikas, Panagiotis and Juan Valcárcel (2016). "The Spliceosome: The Ultimate RNA Chaperone and Sculptor", *Trends in Biochemical Sciences* vol. 41, no. 1 (January), pp. 33-45. doi:10.1016/j.tibs.2015.11.003

Travis, John (2011). "How Does the Cell Position Its proteins?" *Science* vol. 334 (November 25), pp. 1048-49. doi:10.1126/science.334.6059.1048

Wahl, Markus C. and Reinhard Lührmann (2015). "SnapShot: Spliceosome Dynamics I", *Cell*, vol. 161, no. 6, (June 4), pp. 1474-74.e1. doi.org/10.1016/j.cell.2015.05.050

Weiss, Paul (1962). "From Cell to Molecule", in *The Molecular Control of Cellular Activity*, edited by John M. Allen, pp. 1-72. The University of Michigan Institute of Science and Technology Series. New York: McGraw-Hill.

Weiss, Paul A. (1971). *Within the Gates of Science and Beyond: Science in Its Cultural Commitments*. New York: Hafner.

CHAPTER 9

A Mess of Causes

The difficulties in talking about causes in biology have been recognized for over two centuries.[1] It's just that the issues were largely set aside in the era of molecular biology due to the expectation that our rapidly growing powers of minute analysis would bring full causal understanding. 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, the struggle to fit our understanding of living activity into the comfortable garb of familiar causal explanation looks more hopeless than ever.

On one hand, most biologists seem unaware that there is a problem here — or, at least, they are unwilling to betray their awareness in professional circles. On the other hand (as we will see in this chapter), their scientific descriptions could hardly signal more dramatically the failure of the usual causal explanations. We seem to be looking here at another illustration of blindsight.

In Chapter 7 we considered epigenetics, which is commonly taken to be about the way epigenetic "marks" on chromosomes alter gene expression. But no sooner did epigenetics gain biologists' attention than researchers began puzzling over the question, "Do epigenetic marks alter gene expression, or do changes in gene expression alter the marks?" And the question is still with us. According to Luca Magnani, a cancer researcher at Imperial College London,

> It's an absolutely legitimate question and we need to address it. The answer is either going to kill the field [of epigenetics], or make it very important (quoted in Ledford 2015).

"Either kill the field or make it very important". The comment expresses absolute confidence that we can discover unambiguous causation, which will in turn settle the matter: either epigenetic changes *cause* gene activity (in which case they are very important), or they are *mere effects* of that activity, with little significance. It must be one way or the other. The general idea is that, if something is to contribute to scientific understanding, it must be the indisputable cause of an indisputable effect. And yet, as we will now see, this stubborn insistence on causal clarity continually prods biological researchers (we will focus on molecular biology) to offer embarrassingly incoherent explanations.

The seductive appeal of master controllers

Consider the following remarks about a protein known rather blandly as "p53". The remarks issue from a perfectly reputable source who is clearly aware of the subtleties and interwoven intricacies of coordinated, molecular-level activity in the cell. And yet this expert is lured by the mirage of unambiguous causation into offering a wondrously self-annihilating description:

> 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.

To start with, then, we have a *master sensor* (p53) that *controls* various fundamental cellular processes, and yet is itself wholly 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 … (Lu 2010).

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 (as the author goes on to say in the rest of the article) 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.

It is hard to believe that the confusion here is unavoidable. By now every biologist knows how regulatory processes extend outward without limit, connecting in one way or another with virtually every aspect of the cell. But this only underscores the undisciplined terminological confusion continuing to corrupt molecular biological description today. When key regulators are in turn regulated, and controllers have their fates underwritten or redirected by other players, where within the web of mutual interaction 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?

More than an innocent abuse of language

Here is a comment from another paper on p53:

> Following DNA damage, the transcription factor p53 determines whether cells undergo apoptosis [self-induced cell death] or cell cycle arrest and DNA repair. To enable different cellular outcomes, p53 is regulated through its temporal expression dynamics and post-translational modification, and by interactions with chromatin, chromatin regulators and transcription factors.[2]

Here again we have the same terminological confusion, with p53 *determining* cellular outcomes, while it is itself regulated by many pervasive cellular processes. But the authors conclude their paper with these remarkably sensible statements:

> The large number of p53 regulatory mechanisms and their cooperation in triggering specific expression programmes remain open areas for investigation. Systematic measurements in multiple conditions together with models integrating the multiple layers of regulation on p53 activity will be required to decipher the complexity of p53 function.

Why not leave the matter there, with this admirable spirit of openness to the research results as given, together with an acknowledgment of almost unsurveyable complexity? Why are so many researchers driven to paste on top of this picture a contradictory assertion of open-and-shut causal determination?

And I do mean *driven*. How else to explain a comment that could serve as a fitting postscript to our discussion of RNA splicing in Chapter 8. Brenton Graveley, a geneticist at the University of Connecticut Stem Cell Institute, reported in 2011 on the discovery of a splice variant of the protein known as FOX-P1 — a variant that has a role in the generation of stem cells. After usefully elucidating some of what goes on, he offers this as his conclusion:

> What controls the [FOX] splicing switch? What splicing factors are responsible for flipping this switch, and how are their expression and activities regulated? Answering these questions is like hunting down the "chicken-or-the-egg" paradox, but they will ultimately uncover the master regulator of stem cell pluripotency (Graveley 2011).

So in the very act of acknowledging the fundamental "chicken-or-egg" paradox of all biological causation, he reflexively reverts to a kind of creedal affirmation of a still-hidden, but eventually-to-be-found Master Regulator.

If all those who use the language of biologically omnipotent control are really trying to describe something like "important influencers," then that's perfectly fine. But influence is not about mechanism and control; the *things* at issue just don't have controlling powers. Nor, despite Graveley's suggestion, is it about a simple flipping of yes-or-no switches. What we see, rather, is a continual mutual adaptation, interaction, and coordination explicable only in terms of the functional ideas through which we grasp the contextualized *meaning* of what is going on (Chapter 6).

What we see, that is, once we start following out all the interactions at a molecular level, is not some mechanism *dictating* the fate or *controlling* an activity of the organism. Rather (as I have been emphasizing throughout the preceding chapters), we simply observe an organism-wide, narrative coherence — a functional, end-directed, story-like coherence impossible to elucidate from a purely physical point of view. Only so far as they are caught up in this functional story do the individual molecular players find their proper roles.

The misrepresentation of this organic and rational 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.

Biological clocks: who is keeping time?

Pick any topic in biology and you will encounter an egregious failure to “tie down” biological causes. Clockwork mechanisms are nowhere to be found — a fact that becomes particularly poignant in the investigation of “biological clocks” such as the circadian (daily) rhythms that figure so prominently in human and other forms of life. Biologists, of course, set out to identify the “master clock mechanism” that was presumed to “control” these rhythms, and, yes, they found a rhythmic feedback loop involving genes and transcription factors in a certain area of the brain that seemed the perfect candidate. It quickly came to be viewed as the decisive governor of circadian rhythms in the body:

> In mammals, the anatomical structure in the brain that governs circadian rhythms is a small area consisting of approximately 15,000 neurons localized in the anterior hypothalamus, called the suprachiasmatic nucleus (SCN). This “central pacemaker” in the SCN receives signals from the environment and, in turn, coordinates the oscillating activity of peripheral clocks, which are located in almost all tissues (Berger and Sassone-Corsi 2016).

And yet (as this statement already indicates), ongoing research has revealed distinct “clocks” in different mammalian organs and tissues, and indeed in every cell. These “clocks”, it turns out, are not merely on the receiving end of a central, governing coordination, but rather are themselves factors in that coordination, and also, it now seems, are interwoven with just about all aspects of the organism’s physiology — metabolism, reproduction, cell growth and differentiation, immune responses, central nervous system functions …

In each of these areas the quest for causes and master controllers leads to the usual perplexity about who’s doing what to whom. For example: “Although metabolism is thought to be primarily downstream of the cellular clock, numerous studies provide evidence that metabolic cycles can operate independently from or even influence circadian rhythms” (Kumar and Takahashi 2010). At the molecular level, one research team remarks that the enzymatic function of a certain clock protein “may be controlled by changing cell energy levels, or conversely, could regulate them” (Doi et al. 2006). In general: “It seems that connections between the circadian clock and most (if not all) physiological processes are bidirectional” (Yang 2010).

What we’re gaining from all this research is a wonderful portrait of the organism as a rhythmic being. Investigators have not found controlling mechanisms that single-handedly establish or govern the circadian rhythms of the organism, but rather are discovering how those rhythms come to expression at every level and in every precinct of the organism — perhaps more centrally here and more peripherally there, but altogether in a single, organism-wide harmony that is also linked to environmental rhythms. There is no sensible way, as a scientist, to speak of particular mechanisms that *explain* this harmony. Instead, every isolated "mechanism" is found to be a *reflection* of the harmony, and we thereby gain further, detailed understanding of how the whole organism functions as a being in time.

Is any of this a surprise? Should we expect, say, that a "master regulator" of digestion exists? Would it be the stomach? The small intestine? The large intestine? The pancreas? The liver and gall bladder? The metabolism taking place in every cell? The brain that sends various coordinating nervous signals to different organs? The mouth that initiates everything? We would certainly look more to the stomach than, say, to the heart, but the fact remains that the organism as a whole is the closest thing we have to a "master regulator". What we see in the separate, "mechanistic" clocks and regulators of circadian rhythms is simply the functioning of those rhythms in the most recognizable or most focal places. But they merely put on more obvious display the rhythmic functioning of the entire body.

A well-studied worm

Or, we can choose a different example. If there was any place where biologists expected a causal explanation of the organism to emerge clearly, it was in the study of *Caenorhabditis elegans*, a one-millimeter-long, transparent roundworm whose private molecular and cellular affairs may have been more exhaustively exposed than those of any other organism. The adult hermaphrodite has exactly 959 cells, each precisely identified as to origin and type: for example, 302 cells belong to the nervous system. The developmental fate of every somatic cell, from egg to adult, had already been mapped out by 1980. But this mapping and the associated molecular studies did not produce the expected explanations.

Sydney Brenner — who received a 2002 Nobel prize for his work on *C. elegans* — acknowledged that development "is not a neat, sequential process … It's everything going on at the same time". Even regarding the carefully mapped cell lineages of this "simple" roundworm, "there is hardly a shorter way of giving a rule for what goes on than just describing what there is". In other words, the only "rule" for the development of this worm is the entire developmental description of it. When critics suggested he had not really come to an understanding of the worm, but had "only" described it, Brenner responded, "I'm not sure that there necessarily is anything more to understand than what it is" (Lewin 1984).

The difficulties of linear, causal explanation encountered by the *C. elegans* researchers were not accidental. You can't explain an organism of meaning, and you don't need to. You need only allow it, like any meaningful text, to speak ever more vividly and profoundly, in ever greater detail, so as to yield up its unique and unrepeatable story.

The separate processes do not make tidy explanations because they are not really separate and are not doing just one thing. They are harmonizing with everything else that is going on in the organism. We gain understanding when we learn to recognize this harmony in every aspect of the organism. Various analyses can play a crucial role in bringing clarity to our understanding, but the full picture takes shape only when the analytical threads are woven back into the larger fabric of meaning.

Of crosstalk, horror graphs, and collaboration

One final example. Molecular biologists speak about *signals* arriving at *receptors* on the cell surface. The signals are said to bear *messages*, which are then transferred (as it often happens) from the receptors to a series of further *messengers* internal to the cell, which may, among other possibilities, finally convey the message to the cell nucleus. There the message may be *interpreted* to require the increased or decreased *expression* of a gene *coded* for a particular protein. The players in the signaling are, of course, molecules, with proteins being the usual focus of research.

The terminology so naturally resorted to here vividly evokes language, meaning, and communication — something we saw exemplified in Chapter 2. But, of course, this usage is typically treated as "mere metaphor". Signaling pathways have long been regarded as neat, linear sequences of molecular interactions by which an initial encounter — say, the binding of a hormone to a cell membrane receptor — leads to a predetermined result. It's almost as if the language of molecules and cells were merely one of mechanism and logic — not a true language at all.

But the language is in fact much richer than that. Signaling pathways help to maintain a coherence of meaning within and between cells. Take, for example, the work by a team of molecular biologists at the Free University of Brussels. They investigated how signaling pathways interact or "crosstalk" with each other. Tabulating the cross-signalings between just four such pathways yielded what they called a "horror graph", and quickly it began to look as though "everything does everything to everything" (Dumont et al. 2001), much like the way any given term in a meaningful text can modify the meanings of many other terms. Other researchers speak of 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" (Levy et al. 2010).

Even considering a single membrane receptor bound by a hormonal or other signal, you can find yourself looking, conservatively, at a billion possible states, depending on how that receptor is modified by its interactions with other molecules. Despite previous belief, there is no simple binary rule distinguishing deactivated receptors from those activated by some combination of signals in a particular context. "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" (Mayer et al. 2009).

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, turbulent molecular sea of continual exchange that is the cell, and when the cell is one instance of maybe several trillion cells of some 250 different major types in the human body — in muscle and bone, liver and brain, blood and artery — well, it would be understandable if some of those seeking mechanistic or computer-like “controllers” preferred not to stare too long at this 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 influences radiating in all directions as countless local “decisions” are made in a manner somehow disciplined by the immaterial unity (Chapter 6) 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, doesn’t really exist — certainly not as a separate “mechanism”.

In sum: messages are not physically discrete, and they do not fly back and forth as elements of a predefined cellular logic. They move as dynamically sculptured, interwoven patterns of force and energy. Their meanings are mimed or gestured — neither translated into, nor reduced to, a kind of expressionless Morse code, nor impelled along precisely incised channels like computer instructions. And what holds them together amid the ceaseless flow and crosstalk and molecular transformation of the cellular plasm is the unity of meaning that is the whole cell and whole organism. This unity is there for us to observe directly, and we all recognize it, whether with blindsight or otherwise.

Box 9.1 illustrates the problems we’ve been discussing, but does so with specific reference to the molecular biology of gene expression.

Box 9.1

Cause — Or Effect?

In the following quotations, you needn’t worry about the technical details; the general sense of the remarks is all that matters here.

“Technological advances are … revealing an unexpectedly extensive network of communication within and between chromosomes. A crucial unresolved issue is the extent to which this organization affects gene function, rather than just reflecting it” (Fraser and Bickmore 2007).

“Together, these results further emphasize the role for RNA polymerase in shaping the chromatin landscape of the genome and point toward the difficulty in disentangling cause and effect in the relationship between chromatin and transcription” (Weiner et al. 2010, p. 98).

“Epigenetic modifications in Alzheimer’s disease: cause or effect?” — title of a paper. The conclusion: “Further studies are necessary” (Piaceri 2014).

“A long-standing question is whether [cell] replication timing dictates the structure of chromatin or vice versa. Mounting evidence supports a model in which replication timing is both cause and consequence of chromatin structure by providing a means to inherit chromatin states that, in turn, regulate replication timing in the subsequent cell cycle” (Gilbert 2002).

“While several studies using next-generation sequencing have revealed genome-wide associations between epigenetic modifications and transcriptional states, a direct causal relationship at specific genomic loci has not been fully demonstrated …” (Fukushima et al. 2019).

“Despite the difficulties in proving cause and effect, these examples convincingly illustrate how chromatin crosstalk can functionally increase the adaptive plasticity of the cell exposed to the changing microenvironment” (Göndör and Ohlsson 2009).

“A related unresolved question is whether chromatin loops are the cause or the effect of transcriptional regulation” (Deng and Blobel 2010).

“The enthusiasm for establishing whether epigenetic mechanisms link the environment with disease development must be tempered by the knowledge that the epigenome is dynamic and has as much potential to respond to disease as respond to the environment. Therefore it is very difficult to disentangle cause from consequence when studying epigenetic variation and disease” (Relton 2012).

“Despite abundant evidence that most kinds of tumor cells carry so-called epigenetic changes, scientists haven’t yet worked out exactly whether such glitches are a cause or a consequence of disease” (Kaiser 2010).

“The clarification of the cause-and-effect relationship of nuclear organization and the function of the genome represents one of the most important future challenges. Further experiments are needed to determine whether the spatial organization of the nucleus is a consequence of genome organization, chromatin modifications, and DNA-based processes, or whether nuclear architecture is an important determinant of the function of the genome” (Schneider and Grosschedl 2007).

“Although there is widespread agreement that genome form [such as folding and topological domains] and function [gene expression] are intimately connected, their causal relationship remains controversial” (Stadhouders et al. 2019).

“The spatial organization of the genome into compartments and topologically associated domains can have an important role in the regulation of gene expression. But could gene expression conversely regulate genome organization? … Recent evidence suggests a dynamic, reciprocal interplay between fine-scale genome organization and transcription, in which each is able to modulate or reinforce the activity of the other” (Steensel and Furlong 2019).

The problem of causation is fundamental to biology

The powerful compulsion to identify decisive causes, even at the expense of painfully self-contradictory language, strongly suggests that a one-sided and unrealizable ideal of biological explanation is at work. Under its influence we aim to discover a physical lawfulness reflecting, above all, our experience with machines — a lawfulness of precise, unambiguous *control*, where one thing can be said, without unwelcome qualification, to make another thing happen.

Think of a machine. Having conceived what we want it to do, we design it to be a closed system whose intended functioning is more or less immune to contextual interference. And we try to do much the same in many scientific demonstrations. For example, we can create a vacuum in a chamber, and then release a leaf from the top of the chamber. It falls like a stone.

Of course, leaves in nature often travel upward. But the experiment in the chamber enables us to observe the singular and lawful play of gravity, without any disturbing “interference” from the resistance or movement of air. We can then — and only then — say that gravity appears to *make* the leaf fall, just as the simple laws governing the gears and springs of a mechanical watch *make* the watch perform as a reliable keeper of time.

But when the biologist tries to see an animal in the same mechanistic light, as a closed system without interfering factors, the attempt fails miserably. This is because, for the organism, *contextual interference is the whole point*. As the meaning of its activity shifts from moment to moment, so, too, does the contextual significance of all the details of its life.

For example, when a deer is grazing in a meadow, its glimpse of a vaguely canine form in the distance changes the meaning of everything from the flowers and grass the deer was eating, to its own internal digestive processes, to the expression of its genes. This happens, not because the distant form is exerting some strange physical force upon the deer, but because that form becomes part of a now suddenly shifted pattern of meaning.[3]

Or (to focus on the cellular level): when a cell enters into mitosis, just about every detail of its physiology and chemistry takes on an altered meaning in light of the changing narrative context. Everything is now heading toward a new outcome. Molecules that had been participating in one set of interactions (and could easily still do so in purely physical terms) now enter into very different intermolecular relations. Similarly with a cell experiencing heat shock, oxygen deprivation or other stress, a cell coming into contact with new neighbors, or a cell proceeding along a path of embryonic differentiation.

Certainly we can still identify unambiguous causes in the organism. It is always possible to narrow the conditions of our experiments so severely that a consistent “causal arrow” for a particular interaction emerges *under those conditions*. But the whole point of life’s adaptability is to seek *altered conditions* according to present needs and interests. This is why there can be no fixed syntax, no mechanical constancy of relations among the parts. Rather than being a closed system relative to this or that cause, the organism is forever abandoning the coordinating principles of its old context in favor of a new and ever-changing meaning. Its story is always evolving.

I titled this section, “The Problem of Causation is Fundamental to Biology”. The problem I had in mind was that of getting clear about the very nature of causation in biology. It differs from the problem of causation in the physical sciences. Organisms manifest a fluid, integral, harmonizing sort of causation that is more like a play of the multi-dimensional *reasons* for things than a set of one-dimensional mechanical interactions. It is more like the rich interplay of meaning in an unfolding poem than a rigid syntax or logic.

Biologists, on the other hand, seem to be fixated on the “fundamental issue” of distinguishing clear-cut cause from clear-cut effect in the usual physical sense:

> Despite intensive studies of genome organization in the past decade, a fundamental issue remains regarding genomic interactions and genome organization as a cause or a consequence of gene expression. This problem is also pertinent to RNAs, which may have regulatory functions in transcription rather than being simply products of transcription (Li and Fu 2019).

Unfortunately, there is little if any effort to elucidate just what hangs upon this “fundamental issue” — or what might be the implications of the fact that the issue appears irresolvable so long as we insist upon unambiguous physical causation as the basis for biological understanding. For the sake of any who may not yet be convinced about just how thoroughly the problem of cause and effect has bedeviled molecular biologists, I present as a kind of appendix to this chapter Box 9.1, which illustrates the problem with specific reference to the molecular biology of gene expression. (You needn't worry about the technical details; the general sense of the remarks is all that matters here.)

Where are we now?

We Need a Biology Beyond Definitive Causes

If the preoccupation with controlling causes reflects, as I have now suggested, an unrealizable idea of biological explanation, then it also reflects a more or less false understanding of biological reality. I have, in the preceding chapters, been trying to point toward some primary aspects of a more adequate understanding — one that needn't bring us into conflict with what we know. Here is a brief retrospective:

- It has turned out, as we saw in "What Brings Our Genome Alive?" and "Epigenetics: A Brief Introduction", that genes — those supposed *prime causes* of the organism's life — are in fact the focus of almost incomprehensible powers of coordination working from the whole of the cell and organism into the cell nucleus. And the principle of coordination was equally evident in "The Sensitive, Dynamic Cell", where we looked at the membranes and cytoskeleton of cells.
- We have seen, courtesy of the work of the twentieth-century cell biologist, Paul Weiss, that molecules interacting according to physical law in the fluid medium of the cell possess countless "degrees of freedom" that must be curtailed, or disciplined, by the cell as a whole. Similarly, vast numbers of cells must be "held together" according to the functional needs of particular organs. And so, too, the disparate organs and organ systems are harmoniously subordinated to the needs and interests of the organism as a whole. (See especially the chapter, "Context: Dare We Call It Holism?")
- We have also seen (in that same chapter) that biologists incessantly appeal to the "context-dependence" of biological activity. The appeal amounts to a recognition of a kind of causation that works "downward" from the integral unity of a larger whole, into the parts. This causal unity is inseparable from the *ideas* that define a context and hold its elements meaningfully together, thereby posing "The Mystery of an Unexpected Coherence".
- Again, in the present chapter, we have been alerted to the confusion of causes that makes it impossible to explain organisms in the usual causal terms. That is, it is impossible to explain them *biologically* in this way, as opposed to merely elucidating their physics and chemistry. The life-like coordination of physical interactions involves what I referred to above as the "multi-dimensional *reasons* for things rather than a set of one-dimensional mechanical interactions. It is more like the rich interplay of meaning in an unfolding poem than a rigid syntax or logic".
- And, finally, it is hard not to notice that all these themes come together in what we can usefully think of as the organism's story. That is, every organism spins, or

cooperates in spinning, the narrative of its own life. Future-directedness, purposiveness, context-sensitivity, the meaningful interweaving of ideas, the subordination of isolated events and physical causes to the needs, interests, and purposes of active agents — these features that we have noted in organisms are also the features of stories (Chapter 2).

In the next two chapters, dealing with problems of form, we will see how the form of organisms offers us an avenue toward biological understanding that can be a useful corrective to the usual preoccupation with cause and effect. Then, in Chapter 12 ("Is a Qualitative Biology Possible?") we will touch upon the reconceiving of biological causation as a matter of form and idea.

Notes

1. In his 1790 work, *Kritik der Urteilskraft* (subsequently published in English as *Critique of Judgment*), the philosopher Immanuel Kant wrote of the organism that "every part not only exists *by means of* the other parts, but is thought as existing *for the sake of* the others and the whole … also [the] parts are all organs reciprocally *producing* each other" (Kant 1790, Div. 1, para 65).

In speaking of purely physical causation, we certainly would not say that parts exist *for the sake of* each other. But Kant's treatment of these issues was central to a great deal of biological discussion during the following decades — and still surfaces frequently today, at least among philosophers of biology. But the technically oriented training of biologists themselves no longer encourages a familiarity with decisive issues at the foundation of their own discipline.

2. The quotation is from a Table of Contents description in *Nature Reviews Molecular Cell Biology* for Hafner, et al. 2019.

3. I make this same point with the wildebeest and lion in the chapter on "The Organism's Story".

Sources

Berger, Shelley L. and Paolo Sassone-Corsi (2016). "Metabolic Signaling to Chromatin", *Cold Spring Harbor Perspectives in Biology* vol. 8, no. 11. doi:10.1101/cshperspect.a019463

Deng, Wulan and Gerd A. Blobel (2010). "Do Chromatin Loops Provide Epigenetic Gene Expression States?", *Current Opinion in Genetics and Development* vol. 20, pp. 548-54. doi:10.1016/j.gde.2010.06.007

Doi, Masao, Jun Hirayama and Paolo Sassone-Corsi (2006). "Circadian Regulator CLOCK Is a Histone Acetyltransferase", *Cell* vol. 125 (May 5), pp. 497-508. doi:10.1016/j.cell.2006.03.033

Dumont, Jacques E., Fréderic Pécasse and Carine Maenhaut (2001). "Crosstalk and Specificity in Signalling: Are We Crosstalking Ourselves into General Confusion?", *Cellular Signalling* vol. 13, pp. 457-63. doi:10.1016/S0898-6568(01)00168-1

Fraser, Peter and Wendy Bickmore (2007). "Nuclear Organization of the Genome and the Potential for Gene Regulation", *Nature* vol. 447 (May 24), pp. 413-17. doi:10.1038/nature05916

Fukushima, Hiroto S., Hiroyuki Takeda and Ryohei Nakamura (2019). “Targeted in Vivo Epigenome Editing of H3K27me3”, *Epigenetics and Chromatin* vol. 12, no. 17. doi:10.1186/s13072-019-0263-z

Gilbert, David M. (2002). “Replication Timing and Transcriptional Control: Beyond Cause and Effect”, *Current Opinion in Cell Biology* vol. 14, no. 3 (June 1), pp. 377-83. doi:10.1016/S0955-0674(02)00326-5

Göndör, Anita and Rolf Ohlsson (2009). “Chromosome Crosstalk in Three Dimensions”, *Nature* vol. 461 (September 10), pp. 212-17. doi:10.1038/nature08453

Graveley, Brenton R. (2011). “Splicing Up Pluripotency”, *Cell* vol. 147 (September 30), pp. 22-24. doi:10.1016/j.cell.2011.09.004

Hafner, Antonina, Martha L. Bulyk, Ashwini Jambhekar and Galit Lahav (2019). “The Multiple Mechanisms That Regulate p53 Activity and Cell Fate”, *Nature Reviews Molecular Cell Biology* vol. 20, no. 4 (April). doi:10.1038/s41580-019-0110-x

Kaiser, Jocelyn (2010). “Genes Link Epigenetics and Cancer”, *Science* vol. 330, no. 6004 (October 29), p. 577. doi:10.1126/science.330.6004.577

Kant, Immanuel (2000). *Critique of Judgment*, translated by J. H. Bernard. Amherst NY: Prometheus Books. Originally published in German in 1790. Available at https://www.gutenberg.org/ebooks/48433

Kumar, Vivek and Joseph S. Takahashi (2010). “PARP around the Clock”, *Cell* vol. 142 (September 17), pp. 841-43. doi:10.1016/j.cell.2010.08.037

Ledford, Heidi (2015). “The Genome Unwrapped”, *Nature* vol. 528 (December 3), pp. S12–S13. doi:10.1038/528S12a

Levy, Emmanuel D., Christian R. Landry and Stephen W. Michnick (2010). “Signaling through Cooperation”, *Science* vol. 328 (May 21), pp. 983-84. doi:10.1126/science.1190993

Lewin, Roger (1984). “Why Is Development So Illogical?” *Science* vol. 224 (June 22), pp. 1327-29. doi:10.1126/science.6374894

Li, Xiao and Xiang-Dong Fu (2019). “Chromatin-Associated RNAs as Facilitators of Functional Genomic Interactions”, *Nature Reviews Genetics* vol. 20 (September), pp. 503-19. doi:10.1038/s41576-019-0135-1

Lu, Xin (2010). “Tied Up in Loops: Positive and Negative Autoregulation of p53”, *Cold Spring Harbor Perspectives in Biology* (December 9). doi:10.1101/cshperspect.a000984

Mayer, Bruce J., Michael L. Blinov and Leslie M. Loew (2009). “Molecular Machines or Pleiomorphic Ensembles: Signaling Complexes Revisited”, *Journal of Biology* vol. 8, no. 9, article 81. doi:10.1186/jbiol185

Piaceri, Irene, Beatrice Raspanti, Andrea Tedde et al. (2015). “Epigenetic Modifications in Alzheimer’s Disease: Cause or Effect?”, *Journal of Alzheimer’s Disease*, vol. 43, no. 4, pp. 1169-73. doi:10.3233/JAD-141452

Relton, Caroline (2012). “Epidemiology and Epigenetics — A Marriage Made in Heaven?”, *Oxford University Press Blog* (March 28). https://blog.oup.com/2012/03/epidemiology-epigenetics-journal/

Schneider, Robert and Rudolf Grosschedl (2007). “Dynamics and Interplay of Nuclear Architecture, Genome Organization, and Gene Expression”, *Genes and Development* vol. 21, pp. 3027-43. doi:10.1101/gad.1604607

Stadhouders, Ralph, Guillaume J. Filion and Thomas Graf (2019). “Transcription Factors and 3D Genome Conformation in Cell-Fate Decisions”, *Nature* vol. 569 (May 16), pp. 345-54. doi.org/10.1038/s41586-019-1182-7

Steensel, Bas van and Eileen E. M. Furlong (2019). “The Role of Transcription in Shaping the Spatial Organization of the Genome”, *Nature Reviews Molecular Cell Biology* vol. 20, pp. 327-37. doi:10.1038/s41580-019-0114-6

Weiner, Assaf, Amanda Hughes, Moran Yassour et al. (2010). “High-Resolution Nucleosome Mapping Reveals Transcription-Dependent Promoter Packaging”, *Genome Research* vol. 20, pp. 90-100.

doi:10.1101/gr.098509.109

Yang, Xiaoyong (2010). “A Wheel of Time: The Circadian Clock, Nuclear Receptors, and Physiology”, *Genes and Development* vol. 24, pp. 741-47. doi:10.1101/gad.1920710

Chapter 10

What Is the Problem of Form?

It is well known that amphibians such as frogs and salamanders have a remarkable ability to regenerate severed limbs. What may not be so commonly realized is that, if you graft the tail bud of a salamander onto the flank of a frog tadpole at the place where a limb would normally form — and also near the time when metamorphosis of the tadpole into a frog will occur — the grafted organ first grows into a salamander-like tail, and then, in some cases, more or less completely transforms into a limb, albeit a dysfunctional one. Among other changes, the tip of the tail turns into a set of fingers (Farinella-Ferruzza 1956).

The experiment can remind us how biologists commonly try to learn about life by severely disrupting it. But the current point is that, in this particular experiment, the transformation of the tail into an approximate limb cannot be the result of local causes, since the local environment of the fingers-to-be is a tail, not a limb. The power of transformation is, in a puzzling manner, holistic. The part is caught up within the whole and moves toward its new identity based, not merely on local determinants, but also on the form and character of a whole that is *not yet physically all there*.

This may remind us of the rather different experiment we heard Harvard biologist Richard Lewontin describing in Chapter 6: if a researcher excises the developing limb bud from an amphibian embryo, shakes the cells apart, allows them to reaggregate into a random lump, and then replaces the lump in the embryo, a normal leg develops. This shows that the currently unrealized form of the limb as a whole is the ruling factor, redefining the parts according to the larger, developing pattern (Lewontin 1983).

But how can this be? How can spatial position within a not yet fully realized form physically determine the future and proper sculpting of that form, and do so even when parts are surgically switched?

In one way or another, the problem is universal. A key feature of holistic, end-directed, living processes is that the end plays a role in shaping the means. (See many of the preceding chapters, and especially Chapters 2, 6, and 8.) Tadpoles with faces engineered to be highly abnormal “nevertheless largely become normal [adult] frogs: the craniofacial organs move in abnormal paths until a proper frog face morphology is achieved” (Levin 2020). In other words, the means are modified, even becoming entirely unprecedented if necessary, in order to achieve a characteristic result.

We find the same principle when we look at cascades of gene expression, such as the sequential expression of the various genes that have been said to “determine” left-right asymmetry of the vertebrate body. The normal expectation would be that if one blocks or changes the expression of earlier genes in the sequence, the disorder should accumulate and be magnified, perhaps explosively, in downstream gene expression, since proper cues for the later steps are missing. But

> Surprisingly, this is not actually what occurs: each subsequent step has fewer errors than the previous step, suggesting that the classic linear pathway picture is importantly

> incomplete. Embryos recognize transcriptional deviations from the correct pattern and repair them over time … The existence of corrective pathways in embryogenesis and regeneration raises profound questions about the nearly ubiquitous stories our textbooks and “models” tell about the molecular explanations for specific events (Levin 2020).

All this may remind us of E. S. Russell’s remark that in biology “the end-state is more constant than the method of reaching it” (Chapter 2). We also see here the principle that cell biologist Paul Weiss enunciated so clearly at mid-twentieth century, when he pointed out that the whole “*is infinitely less variant from moment to moment than are the momentary activities of its parts*”. At the lowest level of biological activity, molecules in the watery medium of a cell have degrees of freedom (possibilities of movement and interaction) that would spell utter chaos at higher levels if it were not for the fact that the lower-level activity is “disciplined” from above (Weiss 1962, p. 6).

Weiss’ 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. (See also the discussion of Weiss in Chapter 6.)

One further example. During development, the lens of an amphibian eye derives from the outer layer of cells in the developing head, at the point where an outgrowth of the brain comes into contact with the epidermal cells. But if an already developed lens is removed from one of these animals, something truly remarkable happens: a new lens forms from the upper edge of the iris, a structure that has nothing to do with lens formation in normal development. The procedure runs like this (Gilbert 1994, p. 40):

1. Cells from the upper part of the iris — cells that have already reached an endpoint of differentiation — begin multiplying;
2. these multiplying cells then proceed to dedifferentiate — that is, to lose their specialized character, including the pigmentation that gives the iris its color;
3. the newly multiplied, iris-derived cells migrate so as to form a globe of dedifferentiated tissue in the proper location for a lens; and finally,
4. they start producing the differentiated products of lens cells, including crystallin proteins, and are thereby transformed into transparent lens cells — all in the nuanced spatial pattern required for the formation of a proper lens.

And so, lacking the usual resources and the usual context for formation of a lens, the animal follows an altogether novel path toward the restoration of normal form and function.

It is impossible to believe that these complex and intricately coordinated responses to the loss of the lens were somehow already *physically* determined or programmed or otherwise specified in the animal’s one-celled zygote. Nor is it easy to imagine how there could ever have been a sustained and large population of lens-injured amphibians with otherwise functional eyes — a population large enough, that is, to enable a supposedly mindless process of natural selection to evolve a specific, novel solution to the problem of lens regeneration.

The problem of form exists even at the molecular level

The problem of form has long been central to biology, where each creature so notably reproduces after its own kind and according to its own form. “It is hardly too much to say”, wrote geneticist C. H. Waddington, “that the whole science of biology has its origin in the study of form”. In both their descriptive and theoretical activity, biologists "have been immersed in a lore of form and spatial configuration” (Waddington 1951, p. 43).

“Immersed in a lore of form” is, however, an oddly mild way of putting it. “Hopelessly adrift upon a fathomless sea of mystery” might be more fitting. An observer surveying the biological disciplines today (some seventy years after Waddington’s comment) can hardly help noticing that every organism’s stunning achievement of form has become an enigma so profound, and so threatening to the prevailing style of biological explanation, that few biologists dare to focus for long on the substance of the problem.

We will find it necessary in our further discussion to keep in mind that the mystery is at least as apparent on the microscopic (and even the molecular) level as it is at more easily recognizable levels. We have already seen this in earlier chapters. For example, in Chapter 2 we heard the English neurophysiologist, Sir Charles Scott Sherrington, describing how a severed motor nerve in some animals manages to grow back, through many obstacles, toward the far-distant muscle it was originally attached to.

Somehow the minuscule nerve “knows” where it is within the vast three-dimensionality of the animal’s body — knows its own place in contradistinction to that of all the other nerves in different parts of the body. It likewise “senses” where it needs to get to in the local context, and how to find its way there. It’s as if it had a detailed map of the terrain.

When we consider the more general case of wound healing described in Box 10.1, we find ourselves watching how the nerves, blood vessels, muscles, and all the diverse, mangled tissues in a wound sort themselves out. It is all somehow governed by what the description’s author calls “an over-arching sense of the structure of the whole area in which [the] repair takes place”. The original form is restored as far as possible. But what is being sensed? how is it sensed? and “who” is doing the sensing? — these most basic questions remain unanswered.

We saw in Chapter 8 that a similar problem faces us when we look at the several hundred molecules engaged in the intricate molecular “surgery” known as *RNA splicing*. We know that all the complex, carefully sequenced, splicing interactions respect every bit of physical and chemical understanding we have amassed, and so we can explain them in that sense. But a *biological* understanding — an understanding of the effective, flexible, context-dependent coordination of physical events toward a desirable result — remains to be attained.

And so the problem of form, even when we try to approach it at the molecular level, seems intractable from the standpoint of conventional biology. In the case of RNA splicing, we can ask how each of the several hundred molecules cooperating in the activity of splicing is synthesized in the right amount; how each particular molecule is brought to the right place for splicing, and at the right time; how it manages to interact with properly selected molecules among all the other potential partners in the operation, doing so in a carefully choreographed sequence; how the overall co-operation among all the molecules is achieved; and how this cooperation is properly aligned with the *needs* of the cell at a particular time — a time when one form of the spliced RNA rather than another happens to be called for, requiring the "surgery" to be performed with unique variations.

Need is not a term of physical science. Further, all this occurs in a fluid or highly plastic medium, with no crucial and precisely machined channels of communication such as those carved in silicon chips at our high-tech factories. The essential mechanistic constraints, such as those required for the operation of our machines, simply are not there in the organism.

Box 10.1

The Miracle of Wound Healing

Here is a description offered by English biologist Brian Ford (2009):

"Surgery is war. It is impossible to envisage the sheer complexity of what happens within a surgical wound. It is a microscopical scene of devastation. Muscle cells have been crudely crushed, nerves ripped asunder; the scalpel blade has slashed and separated close communities of tissues, rupturing long-established networks of blood vessels. After the operation, broken and cut tissues are crushed together by the surgeon's crude clamps. There is no circulation of blood or lymph across the suture.

"Yet within seconds of the assault, the single cells are stirred into action. They use unimaginable senses to detect what has happened and start to respond. Stem cells specialize to become the spiky-looking cells of the stratum spinosum [one of the lower layers of the epidermis]; the shattered capillaries are meticulously repaired, new cells form layers of smooth muscle in the blood-vessel walls and neat endothelium; nerve fibres extend towards the site of the suture to restore the tactile senses …

"These phenomena require individual cells to work out what they need to do. And the ingenious restoration of the blood-vessel network reveals that there is an over-arching sense of the structure of the whole area in which this remarkable repair takes place. So too does the restoration of the skin. Cells that carry out the repair are subtly coordinated so that the skin surface, the contour of which they cannot surely detect, is restored in a form that is close to perfect."

Of course, researchers have traced all sorts of molecular syntheses, movements, and interactions. We can be sure that everything in the entire picture proceeds lawfully, and in this very constricted sense every local event looks necessary. And yet we can find no combination of physical laws capable of "enforcing" the proper form of all the different parts of the body of this or that animal. In the case of a wound, there is no purely physical necessity to achieve a given form in the face of unpredictable conditions.

In other words, the mere fact of physical lawfulness does not explain the *coordination of events* along an extended timeline in the narrative of healing, from infliction of the wound to the final restoration of normalcy. Nor does it explain the narrative of RNA splicing, from the occurrence of an RNA molecule in need of reconfiguration, to the final product of those hundreds of participating molecular “surgeons”. We can watch the molecules performing in a way that gives expression to the overall sense, or meaning, of the activity, but we do not have even the barest beginnings of a purely physical explanation for their commitment to that meaning.

Michael Levin: Revolutionary

I wrote above that every organism’s stunning achievement of form has become an enigma so profound, and so threatening to the prevailing style of biological explanation, that few biologists dare to focus for long on the substance of the problem. Michael Levin is one of those few. An enthusiastic, prolific, hyper-achieving researcher, he appears to represent at least part of the future of biology. As the Vannevar Bush Professor at Tufts University near Boston, Levin is principal investigator of the Levin Lab there, director of the Tufts Center for Regenerative and Developmental Biology, and team leader of the Allen Discovery Center at Tufts. He also holds positions at Harvard and MIT. The wide-ranging work under his supervision includes pioneering explorations of the role of electrical fields in the production of biological form. (See Box 10.2.)

But what is perhaps most impressive about Levin is his willingness at least to make a start at acknowledging certain extraordinarily difficult questions biologists must raise if they want to face organisms squarely, as we actually observe them. Chief among these is the problem of organic form.

Levin is particularly explicit about this problem in a paper entitled “The Biophysics of Regenerative Repair Suggests New Perspectives on Biological Causation”, published in *Bioessays* (Levin 2020). We will now give particular attention to this paper, which will be the source of all quotations unless otherwise indicated.

The way in which tissue voltage patterns prefigure the developing form of embryos has been central to Levin’s thinking (Box 10.2). This prefiguring, he emphasizes, is not in the first instance a genetic event, but “a [much higher-level] physiological event … causally responsible for a given patterning outcome” — and therefore also a cause of the gene expression required for that outcome.

In other words — and this is where Levin particularly sees himself offering something new — there is a kind of causation, somehow active in the larger pattern, that we cannot understand by adding together the causal action of molecular-level entities upon each other. The tissue-wide electric potentials can fairly be said to play a decisive role in stimulating cascades of gene expression on the way toward formation of entire organs. But, in the reverse direction, genes cannot be said to cause, or explain, the patterns of electric potential.[2]

Similarly with the examples in the opening section of this chapter. They all raise the problem of causation from whole to part — and (although this is not a point Levin raises) they all vex our efforts at strictly physical understanding. The question we need to ask ourselves is this: “How can the physical body of a relatively undeveloped organism — a body already exhibiting coordinated physical processes perfectly adapted to the organism’s present state — redirect and transform those well-adapted physical processes so as to conform to a different and more “mature” pattern that is not yet there?”

Whole-part, future-oriented causation

Why does holistic causation refuse strictly physical understanding? A key difficulty, as I have been emphasizing, lies in the observation that every embryo seems, in its holistic manner, to be *reliably guided* toward a future state. It is as if that future state were somehow present and influential along the entire path of its own material realization — as if the developing embryo were expressing from the very beginning its own *telos*, or the essential idea of its ultimate maturity and wholeness, as a very real and present power.

Box 10.2

Electricity in the Developing Tadpole

In the summer of 2011 a team of researchers at Tufts University produced a startling, time-lapse video of a developing tadpole embryo.[1] Due to the use of special dyes reporting the electric potentials across cell membranes, areas of the embryonic surface successively lit up brightly and then went dark. For a few seconds of the time-lapse film (representing the events of several hours), the featureless part of the embryo that would eventually become the animal’s head flashed the image of a tadpole face.

But no actual face had yet developed. Nevertheless, the electrical pattern did “signal” where key elements of the tadpole’s face, such as its eyes, would eventually appear. Regional changes in electric potential, these scientists concluded, “regulate expression of genes involved in craniofacial development”.

According to Michael Levin, head of the laboratory where the tadpole research was performed, “Ion flows and the resulting [membrane voltage] changes are components of long-range conversations that orchestrate cellular activities during embryonic development, regeneration, and … tumor suppression”. He adds that “bioelectric cues are increasingly being found to be an important regulator of cell behavior”, controlling the proliferation and death of cells, their migration and orientation, and their differentiation into different cell types.

“We are”, he wrote further, “just beginning to scratch the surface of the bioelectric code — the mapping between voltage properties and patterning outcomes, akin to the genetic, epigenetic, and perhaps other codes remaining to be discovered” (Levin 2012).

Levin’s team quickly went on to manipulate the distribution of membrane voltages in developing embryos so as to provoke the generation of eyes in decidedly unexpected places — for example, on the back and tail, and even in the gut, of a frog embryo. The results were fragmentary and rather chaotic — the ectopic (“out of place”) eyes were partial or deformed — but the result was nevertheless as startling as it was monstrous (Pai et al. 2012).

In a moment we will have to ask to what degree Levin clearly recognizes how thoroughly the problem of causation running from whole to part and directed toward the future disrupts conventional thinking. He is, in any case, fascinated by what he often refers to as “top-down causation” — “an important distinct type of causation” in which ”a future state … guides the behavior of the system”. He recognizes the “incredibly tangled details underlying system-level outcomes in biological systems”, and instead of immediately pivoting away from the challenge of future-directed, higher-level causation in order to resume the analysis of microstates, he questions the wisdom of such a strategy:

> Embryonic patterning, remodeling, and regeneration achieve invariant anatomical outcomes despite external interventions. Linear "developmental pathways" are often inadequate explanations for dynamic large-scale pattern regulation, even when they accurately capture relationships between molecular components.

That is, even in the face of the researcher's deranging intrusions, the embryo does its best to re-organize itself in the light of a characteristic outcome yet to be fully realized — all in a way that does not seem to be explained by the activity of lower-level entities.

The common expectation, which dominated twentieth-century molecular biology, had been that we would learn to track every microstate in every cell and organism, and in doing this we would gain all the understanding of biological processes we could ask for. Levin wonders whether this expectation isn't having the unfortunate effect of "delaying the development of higher-level laws" that could advance our interests more effectively.

So, then: what might he mean by "higher-level laws"?

Michael Levin: Counter-revolutionary

Levin has seen deeply into decisive and overlooked problems of biology. This means that — and I intend no derogation of his profound insights in saying so — it is particularly revealing of the state of modern biology to see how conventional dogma sets bounds to the solutions he can conceive. Despite his desire to frame a new paradigm of causation in living beings, his work does testify to the deeply engrained power of conventional biological thinking. In fact, at times he seems drawn to the most abstract and least biological aspects of this thinking.

Counter to what you might have thought based on the preceding descriptions, Levin's interests center emphatically on *machine-like* models, *control*, and *prediction*. (I count forty-eight occurrences of the word "control" in the main body of his article.) He repeatedly expresses his confidence in explanatory models based on "top-down" techniques already "exploited very successfully by control theory, cybernetics, computer science, and engineering of autonomous robotics" — and is also impressed by "new developments in information theory that help to rigorously identify and quantify tractable macrostates with maximal causal power". These top-down tools of control could now "enable transformative advances in biomedicine".

By "top-down" Levin typically means: driven by something like an engineer-designed computer program embodied in things like circuits and switches. The *new* in his "new paradigm" consists largely of the fact that the program is thought to be (somehow) distributed throughout tissues and organs, rather than encoded in the tight "logic" of the DNA sequence.

Even the bioelectric features of tissues (Box 10.2) become, for Levin, the manifestations of digital devices. When he looks at these features, he sees circuits, biolectric networks that serve as “a rich computational medium”, and feedback loops “equivalent to transistors — fundamental building blocks of logic circuits and decision-making machinery”.

And so, he is convinced, appropriate machine models present a wonderful opportunity: we may gain “predictive control in regenerative medicine and synthetic biology”. All that is required is a high-level focus on “control mechanisms that harness cell behavior toward specific organ-level outcomes”. His complaint about microstates as presumptive causes is that they do not enable us “to make quantitatively accurate predictions with respect to the complex final outcome … which is the key property we require from a purported explanation of a biological process”.

One might have thought that at least one key thing we want from biological explanations is an understanding of the unique, qualitative ways of being distinguishing the life of one organism from another — for example, the zebra from the lion (Holdrege 2020). The narrow interest in “quantitatively accurate predictions”, on the other hand, stems from the long-running commitment of science to the discovery of clear and unambiguous causes of a certain sort — reliable causal factors that, within carefully controlled systems, *consistently make specific things happen*, and therefore can be used technologically.

Certainly we do want a maximally *effective* medicine, just as we want a maximally effective political or educational system. But this does not mean we can healthily understand political or educational processes by grounding ourselves in machine models of causation. And the same goes for medicine.

The main problem we have in following Levin is that we arrive at neither a revolution nor a new paradigm for causation merely by changing our level of observation from microstates to macrostates — from molecules to tissues and organs. As long as we remain committed to the same physical and mechanistic notion of causation that has dominated biology for the past few centuries, we can hardly claim to have arrived at a profoundly new understanding of biological causation.

I believe Levin has glimpsed the fact that something radically changes when one begins to talk about top-down causation — especially if one realizes that, in organisms, we are looking not only at causes running from the whole toward the parts, but also at a kind of future-oriented causation. But he has compromised this insight by forcibly marrying it to tired, machine-based habits of explanation that represent nothing but the old paradigm.

Of course, he might well object to this. His references to cybernetics, control theory, and computational neuroscience show that he sees himself focusing on a *distinct type* of machine — namely, those operating under some form of programmed control and feedback. Don’t we see in these machines a kind of top-down and purposive causation that seems to match that of organisms? The inadequacy of current thinking about biological causation, he is suggesting, lies in biologists’ failure to exploit the analogies between living beings, on one hand, and machines *of this particular sort*, on the other.

He is right — and importantly so — about biologists’ failure to take seriously the fact of purposive biological processes. But does he himself fully acknowledge the purposive dimension of organic activity? Or does he instead think in terms of activity that only *looks*, rather illusorily, "as if" it were purposive? And do programmed machines point us toward a useful understanding of biological causation?

In what sense are machines end-directed?

In his paper, Levin addresses the idea of "setpoints as causes". Setpoints, he says, are not-yet-existing "future states" that somehow "guide the behavior of the system" toward a realization of those future states. As it stands — and in relation to living beings — the assertion is as vague as it is radical. But Levin makes clear the kind of thing he has in mind: it is illustrated above all by the kind of feedback and control systems we routinely rely upon in devices we use daily.

In such systems, the setpoint is embodied in a mechanism or controller that can be set to some value. In a very simple case, this could be a thermostat set to a particular temperature. That temperature is the setpoint, and the thermostat uses it to control a heating system, such as the one in many homes.

A more complex case would be a computer taking input from buttons you may have on your automobile's steering wheel, where the input represents a desired cruise control speed. Or think of a cruise missile flexibly seeking out a specified target with the help of "sensing" instruments and a complex, computerized guidance system. The target (set point) must, in one way or another, be entered into the computer.

It is obvious that we can say, abstractly and analogically, that organisms pursuing their own purposes have "setpoints". The lion (in some sense) races "like" a cruise missile toward the antelope, adjusting its course as the antelope turns this way and that. And, likewise, the lion embryo flexibly pursues a reliable "trajectory" toward its mature form. But — although Levin often seems to forget the fact — such remote analogies fail to show that the lion can in any meaningful sense be explained as the functioning of a programmed machine. This would have to be demonstrated.

Surely (to change the image) it is difficult to find much commonality between the transformation of a single zygotic cell into a mature eagle, on one hand, and the "development" of a missile, on the other. If, before venturing upon its flight, the missile were to "mature" from a single transistor (or circuit board) into the totality of a functioning, deadly efficient vehicle; and if, during its flight, all its physical constituents were metabolizing and metamorphosing as an essential part of the overall operation; and if, instead of a single "setpoint", there were a massively interwoven and nearly infinite collection of "setpoints" governing each of the missile's "organs", each "cell", the entire missile as a whole, and all its environmental relations — well, as you can see, taking the comparison with living beings seriously could get silly fast.

In any case, the decisive issue is not difficult to grasp. Cruise missiles — and, for that matter, kitchen blenders, electric hand drills, and textile looms — consist of materials we articulate together for use as tools in accomplishing our own tasks. The "top-down" ideas guiding assembly are ours; they do not come to expression through holistically active developmental processes in which all the parts being assembled participate. *Our* ideas are not native to the collection of parts. Our ideas are not active at the very root of material manifestation in the way that physical laws and biological principles are inseparable from the substance in which they work. We merely rearrange, in an external manner, materials already given to us. We cannot penetrate to the inherent lawfulness of physical materials with the force of our wills, except in moving our own bodies. (And even there, the doing is currently inaccessible to our understanding.[3])

When we want to explain the operation of a kitchen blender (or a missile), we require no reference to its intentions, or to any striving toward a future state. When we do make such reference, we are really talking about our own purposes in structuring the device for employment in service of our interests. There is no more an *immanent* end-directness in a cruise missile than in a blender. Both devices are simply put together in accordance with *our* purposes.

By contrast, a developing organism's living "trajectory" results from its *growing* directionally into its mature functioning. We never see a designing power or force that assembles an organism from pre-existing parts in anything like the way we build tools and machines. *Organisms are not designed and tinkered with from without, but rather are enlivened from within*. The wisdom we find at play in them is intrinsic; it is their own in a sense wholly untrue of the external intelligence with which our mechanical inventions are structured.[4]

Does this not make a great difference for our thinking about causation in organisms and machines? The act of structuring and programming a physical device such as a cruise missile is our own. The missile itself has no intentions, and is not "aiming at" anything, no matter how great our role as inventors and builders. In this regard it is simply a more complex kitchen blender. We may have gotten more sophisticated in shaping tools to our own ends, but that is our development, not the machine's.

A deep issue, unaddressed

I have several times mentioned in these pages that all biologists do recognize the agency — the *telos*-realizing, purposive, task-oriented, and storytelling (narrative) activity — of organisms. Biological research is structured by our interest in the things organisms do and accomplish so differently from what rocks "do" and "accomplish", from gene expression, to DNA replication and cell division, to growth and development, to animal behavior.

But, as I have also mentioned, this awareness of agency remains, for most biologists, blindsighted, and therefore does not make its way into biological theory and explanation, or even into the biologist's own clear consciousness. Levin therefore provides a valuable service by encouraging a more general awareness of what he occasionally refers to as the "teleological" dimension of biology.

I do regret, however, that despite his extraordinarily wide-ranging familiarity with the technical literature, he shows no evidence of having mined the rich wisdom in the works of the organicist biologists of the twentieth century — figures such as E. S. Russell and John Scott Haldane (not to be confused with his son, J. B. S. Haldane) in Britain, and Paul Weiss in

America.[5] These prominent and well-respected researchers had already grasped the centrality for biology of the coordinating ("top-down") agency at work in organisms seen as wholes.

A familiarity with this earlier work might have prodded Levin to take a more critical approach to the machine models he so insistently applies to organisms. As it is, he makes no very apparent effort to justify a substantive comparison of living activity to humanly designed machine operation. He does, however, assure us that, with respect to developing organisms, "work is ongoing to understand the molecular nature of the processes that measure the [current] state, maintain the setpoint, and implement the means-ends process to achieve the target morphology".

But, in the work he cites, I see nothing to suggest answers to the most obvious questions. Where might the setpoint be physically embodied — where might it even *conceivably* be embodied — so as to represent the entire, infinitely detailed and intricately interwoven morphology of a given animal? Once found, how might this setpoint actually direct and coordinate all the animal's living activity over a lifetime — or over a single healing episode such as described in Box 10.1? And where do we find evidence that an organism's fundamental activity of *growth*, *striving*, and *self-transformation* can be understood on the model of our technological devices?

Much of the work Levin draws upon to illustrate machine-based theorizing about the top-down performance of organisms comes from neuroscience, and especially computational neuroscience. The naïveté expressed in this work can be startling. This is illustrated by how quickly, in the dawning computer age, neuroscientists decided that neurons (the only cells in the brain taken with any seriousness at the time) were essentially binary, on-or-off devices more or less like transistors. Even today that basic mind-set seems entrenched, despite the inevitable complicating factors emerging year after year.

It all reminds me of the prominently honored theoretical neuroscientist, Larry Abbott, who, in a genuine attempt to support the prevailing mindset, wrote a book chapter about the brain entitled "Where Are the Switches on This Thing?" (Abbott 2006). There turns out to be no obvious answer.

Beyond neuroscience, it seems that if anyone anywhere has applied a machine model to biological problems, and if the machine model incorporates a top-down aspect, as in cybernetic devices, this seems enough for Levin to claim an applicability to organisms and a confirmation of top-down living activity. But why the need for such confirmation in machine-based models, when the most obvious route to it is simply to *look* at organisms, as eminent biologists have already done — and as all biologists do, at least unconsciously? The problem of *telos*-realizing activity is universally recognized, even if nearly all biologists assume it has somehow been explained away by natural selection.

An unquestioned model

The machine model seems so deeply embedded in Levin's thinking that one can only surmise he has never thought of questioning it. He seems to think it inevitable that any analogy between an organism and a machine, however abstract, means the organism must work the way the machine works. He is properly struck by the remarkable achievements of development and regeneration we mentioned earlier in this chapter. But when he looks at these achievements, he immediately, and without further question, sees in them "extensive proof-of-principle of control circuits that enable efficient self-repair and dynamic control of multicellular, large-scale shape" (Pezzulo and Levin 2015).

In other words, the fact that we see the organism developmentally transforming itself and healing wounds — and doing so as a coherent whole — is already proof for him that we are dealing with large-scale "control circuits". Certainly there *is* a physical activity through which the organism's transformation and healing are realized. But nowhere in the physical lawfulness of this activity do we find the requisite principles of coordination and control. The fact that we can build machines with certain kinds of controls does not show that organisms function causally in the manner of these machines.

As for the *predictability* in which Levin sees evidence of top-down controls, his prime illustrations are the achievement of his laboratory in stimulating the development of eyes on the tails (or in the guts) of tadpoles, and in producing two-headed flatworms — all by means of bioelectric manipulations. It is true enough that when we forcibly intervene in an animal's life, giving it biological signals that would not normally occur, it can only take the signals as reality and respond holistically as best it can. Presumably, if we intervene to keep experimental conditions constant, we might (more or less predictably) expect similar insults to produce similar responses.

But it isn't clear how "throwing a wrench into the works" by deranging an animal's normal developmental processes, thereby causing the formation of dysfunctional eyes and supernumerary heads, constitutes the kind of predictability we would want from an understanding of the *true nature* of an organism. And, in any case, none of this testifies to the machine-like nature of the processes by which an organism carries out even deranged living activities.

It is precisely *because* every organism is, in a holistic sense, an agent, that it can respond to violent interventions in a meaningful and creative manner. This holistic response is what seems to entrance Levin. He wants other biologists to recognize the organism's top-down performance. But not only does he fail to reckon with the work of earlier biologists who both described such holistic agency *and* denied the machine interpretation; he sees no need to make his own case for that interpretation. He just takes it for granted.

Given his promise as a biologist, I could dearly wish that Levin would consider something like the process of RNA splicing described in Chapter 8, or DNA replication and damage repair, or cell division, or just about any other sustained biochemical or physiological activity in living beings. And then I would love to see him view this activity in light of the observation by Paul Weiss we heard above: The behavior of the whole "is infinitely less variant from moment to moment than are the momentary activities of its parts”. Where are the machine models that can meaningfully elucidate the overall *coherence* of these largely fluid phenomena?

I am sure Levin would be pleased to see how Weiss’ work thoroughly supports his own interest in top-down causation. And I suspect that he would recognize the wisdom in Weiss’ refusal of machine-based explanation.

Where are we now?

Organic Form and Machine Models

We have been introduced to the problem of form — the problem Michael Levin so eloquently brings to the biologist’s attention. How does an organism move in a persistent, adaptive, and sometimes strikingly novel way toward the realization of a living shape and functioning that are in some sense “given in advance”? Levin has clearly seen that this sort of activity, like purposive or future-oriented activity in general, requires us to recognize a kind of causation that somehow works not only from the present into the future (or, perhaps better, from the future into the present), but also from the whole into its parts.

But we also see in Levin’s response to this problem the remarkable and seemingly unshakable power of machine-based thinking in contemporary biology, especially as exemplified in computers. Having effectively posed questions that could radically re-shape today’s biology, he is content to return to the worst tendencies of the life sciences. As I have tried to show in this and the preceding chapters, the machine model fails the organism at virtually every point of comparison. Nor is the matter particularly subtle. It does not require much insight to see that the notions of wired cells, master controllers, computer-like instructions conveyed from here to there, or inert, unliving, machine-like parts coming together to form a living cell or organism simply don’t carry any convincing weight.

In sum, machine-based ideas are neither revolutionary nor particularly helpful for our approach to questions concerning the character of biological activity.

In the next chapter we will look at another take on the problem of biological form — the one offered by evolutionary developmental biologist Sean Carroll in his book, *Endless Forms Most Beautiful*. He, too, is enamored of machine- and computer-based thinking. But his way of approaching the problem of form will enable us to get at a rather unexpected conclusion: form is not something we should be feeling a need to explain, least of all to explain with our familiar mechanistic notions. Once we rise above those notions, we may be able to gain our first glimpse of a game-changing question: Might it be that the proper apprehension of form is itself the understanding we were really seeking all along?

Notes

1. Vandenberg et al. 2011. As of April, 2020, the video was available here.

2. The point is that bioelectric fields across tissues are the result of physiological processes at a considerable remove from gene expression. While genes are certainly required for the production of the ion-transporting proteins that help produce electric fields, these genes can hardly be said to control the subsequent activity of these proteins. This activity includes the elaborate and sensitively shifting play of bioelectric signaling of the sort involved in craniofacial patterning of the tadpole.

3. We may also bring materials into contact with each other so that they can undergo the chemical transformations expressing their own inherent potentials. These transformations, such as the (sometimes explosive) reaction of gaseous oxygen and hydrogen to produce water, remain almost a complete mystery to us at the qualitative, phenomenal level, despite our ability to map forces and create models of (falsely imagined) “entities” at the atomic and molecular levels.

4. The poet and philosopher, Samuel Taylor Coleridge, captured the distinction between machine and organism very well when he wrote:

> The form is mechanic when on any given material we impress a predetermined form, not necessarily arising out of the properties of the material — as when to a mass of wet clay we give whatever shape we wish it to retain when hardened. The organic form, on the other hand, is innate; it shapes as it develops itself from within, and the fullness of its development is one and the same with the perfection of its outward form. Such is the life, such is the form (quoted in Guite 2017, p. 365).

The original source is given as *Lectures 1808-1819 on Literature*, by Samuel Taylor Coleridge, edited by R. A. Foakes, vol. 1, p. 495.

5. See, for example, Weiss 1962, Weiss 1968, Weiss 1973, Russell 1930, Russell 1945, Russell 1938, Haldane 1917, and Haldane 1923.

Sources

Abbott, Larry F. (2006). “Where Are the Switches on This Thing?”, in J. L. van Hemmen and T.J. Sejnowski, editors, *23 Problems in Systems Neuroscience*. Oxford: Oxford University Press.

Farinella-Ferruzza, N. (1956). “The Transformation of a Tail into Limb after Xenoplastic Transplantation”, *Experientia* vol. 12, pp. 304-5. https://doi.org/10.1007/BF02159624

Ford, Brian J. (2009). “On Intelligence in Cells: The Case for Whole Cell Biology”, *Interdisciplinary Science Reviews* vol. 34, no. 4 (December), pp. 350-65. doi:10.1179/030801809X12529269201282

Gilbert, Scott F. (1994). *Developmental Biology*, 4th edition. Sunderland MA: Sinauer Associates.

Guite, Malcolm (2017). *Mariner — A Voyage with Samuel Taylor Coleridge*. London: Hodder and Stoughton.

Haldane, John Scott (1917). *Organism and Environment as Illustrated by the Physiology of Breathing*. New Haven: Yale University Press.

Haldane, J. S. (1923). *Mechanism, Life and Personality: An Examination of the Mechanistic Theory of Life and Mind*, second edition. London: John Murray. Facsimile of second edition published in 1973 by Greenwood Press, Westport CT.

Holdrege, Craig (2020). “The Intertwined Worlds of Zebra and Lion”, *In Context* # 43, pp. 12-19. https://natureinstitute.org/pub/ic/ic43/zebralion.pdf

Levin, Michael (2012). “Molecular Bioelectricity in Developmental Biology: New Tools and Recent Discoveries”, *Bioessays* vol. 34, pp. 205-17. doi:10.1002/bies.201100136

Levin, Michael (2020). “The Biophysics of Regenerative Repair Suggests New Perspectives on Biological Causation”, *BioEssays* vol. 42, no. 2 (February). doi:10.1002/bies.201900146

Lewontin, Richard C. (1983). “The Corpse in the Elevator”, *New York Review of Books* vol. 29, no. 21 (January 20), pp. 34-37. https://www.nybooks.com/articles/1983/01/20/the-corpse-in-the-elevator/

Pai, Vaibhav P., Sherry Aw, Tal Shomrat et al. (2012). “Transmembrane Voltage Potential Controls Embryonic Eye Patterning in *Xenopus laevis*”, *Development* vol. 139, pp. 313-23. doi:10.1242/dev.073759

Pezzulo, Giovanni and Michael Levin (2015). “Re-membering the Body: Applications of Computational Neuroscience to the Top-down Control of Regeneration of Limbs and Other Complex Organs”, *Integrative Biology*. doi:10.1039/c5ib00221d

Pezzulo, Giovanni and Michael Levin (2016). “Top-down Models in Biology: Explanation and Control of Complex Living Systems Above the Molecular Level”, *Journal of the Royal Society Interface* vol. 13, 20160555. https://doi.org/10.1098/rsif.2016.0555

Russell, E. S. (1930). *The Interpretation of Development and Heredity: A Study in Biological Method*. Freeport NY: Books for Libraries Press.

Russell, E. S. (1938). *The Behaviour of Animals*. London: Edward Arnold. Second edition.

Russell, E. S. (1945). *The Directiveness of Organic Activities*. Cambridge UK: Cambridge University Press.

Vandenberg, Laura N., Ryan D. Morrie and Dany Spencer Adams (2011a). “V- ATPase-Dependent Ectodermal Voltage and pH Regionalization Are Required for Craniofacial Morphogenesis”, *Developmental Dynamics* vol. 240, pp. 1889-1904. doi:10.1002/dvdy.22685

Waddington, C. H. (1951). "The Character of Biological Form", in *Aspects of Form: A Symposium on Form in Nature and Art*, edited by Lancelot Law Whyte, preface by Herbert Read. Bloomington IN: Indiana University Press, pp. 43–52.

Weiss, Paul (1962). “From Cell to Molecule”, in *The Molecular Control of Cellular Activity*, edited by John M. Allen. The University of Michigan Institute of Science and Technology Series. New York: McGraw-Hill, pp. 1-72.

Weiss, Paul (1963). “The Cell as Unit”, *Journal of Theoretical Biology* vol. 5, pp. 389-97. doi:10.1016/0022-5193(63)90085-7

Weiss, Paul A. (1968). *Dynamics of Development: Experiments and Inferences*. New York: Academic Press.

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

Chapter 11

Why We Cannot Explain the Form of Organisms

Questions of form have seemed oddly resistant to the biologist's quest for explanation. Darwin himself seemed to sense the difficulty in that famous instance where he recoiled from contemplating the subtle perfections in the form of the eye: "To suppose that the eye with all its inimitable contrivances for adjusting the focus to different distances, for admitting different amounts of light, and for the correction of spherical and chromatic aberration, could have been formed by natural selection, seems, I freely confess, absurd in the highest degree" (Darwin 1859, chapter 6).

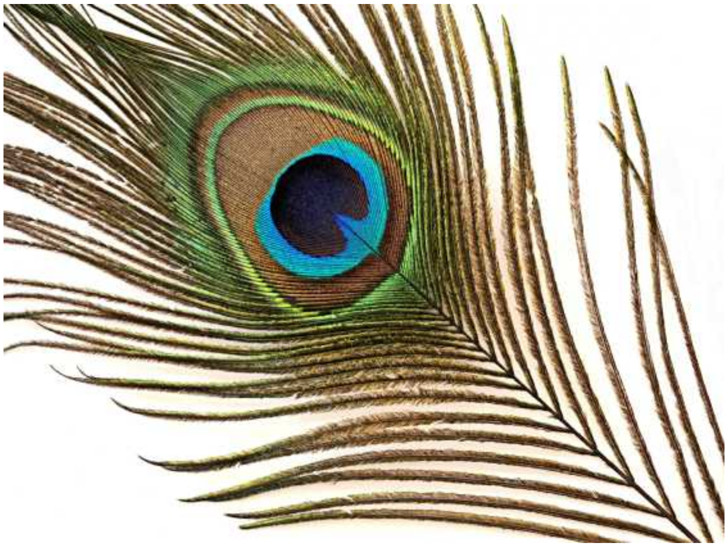

Figure 11.1. An eyespot in a peacock feather.

Of course, as Darwin quickly added, his theory convinced him that he was merely suffering from a lack of imagination. All that was really needed were the creative powers of natural selection acting through eons upon an endless supply of small, helpful changes. But his underlying malaise was not so easily vanquished: "It is curious", he wrote to the American botanist Asa Gray in the year following publication of the *Origin*, "that I remember well [the] time when the thought of the eye made me cold all over, but I have got over this stage of the complaint, and now small trifling particulars of structure often make me very uncomfortable. The sight of a feather in a peacock's tail, whenever I gaze at it, makes me sick!" (Darwin 1860).

We can assume that Darwin got over that stage of the complaint as well. But, thankfully, the biologist is still now and then allowed, if not a complaint, at least an honest expression of wonder. The great twentieth-century student of animal form, Adolf Portmann, writing not of the peacock, but of another bird with a remarkable pattern of coloration on its wings, helps us to share in his own wonder:

> If … we look at the speculum on a duck's wing, we might imagine that an artist had drawn his brush across some ten blank feathers, which overlap sideways — making white, bluey-green, and black lines — so that the stroke of the brush touched only the exposed part of each feather. The pattern is a single whole, superimposed on the individual feathers, so that the design on each, seen by itself, no longer appears symmetrical. We realize the astonishing nature of such a combined pattern only when we consider that it develops

> inside several or many feather sheaths completely separated from one another; and that in each individual feather it appears at an early stage while it is still tightly rolled up, the joint pattern not being produced until these feathers are unfolded. What sort of unknown forces direct the constructional work in the “painting” of these feather germs? (Portmann 1967, p. 22).

Whatever Portmann’s “unknown forces” may be, they seem to work to perfection. But how are we to understand this perfection? What sort of explanation are we looking for when we want to make *sense* of form? In the case of that patch of color on the duck’s wings, surely we will eventually be able to trace exhaustively the processes and connections by which each molecule of pigment seems lawfully “compelled” to take up its proper place in the various feathers. But where, amid the innumerable, widely dispersed molecular jigglings, transits, collisions, interactions, and chemical transformations, will we glimpse the global *coordinating* power that guarantees the overall, aesthetically satisfying outcome in the face of all the degrees of freedom (Chapter 6) possessed by the interacting molecules in all the individual and separate feathers?

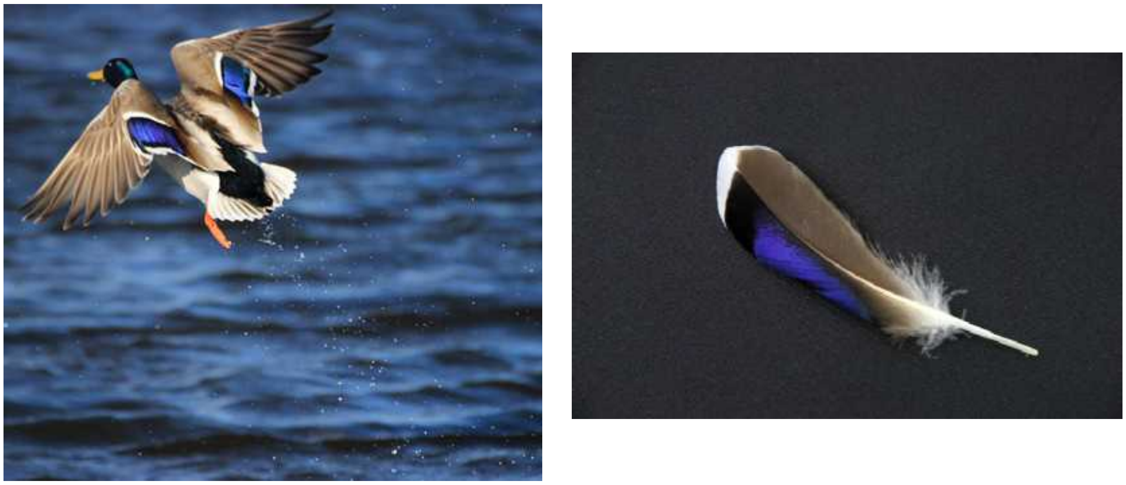

Figure 11.2. A mallard duck with a speculum on each of its wings (left); and an individual speculum feather (right).[1]

Looking for physical explanations of form

Sean Carroll thinks he has an answer to this question. A geneticist and developmental biologist, Carroll tells the story of the rising discipline of evolutionary developmental biology in a widely read and beautifully illustrated book, *Endless Forms Most Beautiful: The New Science of Evo Devo* (Carroll 2005). Inspired by work in the relatively young discipline of evolutionary developmental biology (“evo devo”), he aims to explain “the invisible genes and some simple rules that shape animal form and evolution” (p. x).

Carroll’s triumphalist narrative focuses heavily on the role of “tool kit” or “master” genes. (On “master” controllers in general, see Chapter 9, “A Mess of Causes”.) Until the discovery of these genes, he tells us, biologists had known that “evolution is due to changes in genes, but this was a principle without an example. No gene that affected the form and evolution of any animal had been characterized” (p. 8).

That state of affairs apparently ended with the identification of a relatively small number of genes whose presence, absence, or mutation turned out to be associated with the formation (or deformation) of large-scale, discrete features of an organism — and they were often associated with similar features in widely differing organisms. These tool kit genes may, for example, produce proteins that are distributed in bands, stripes, lines, or spots throughout a young insect embryo. This geographical distribution turns out to be a kind of map of certain, large-scale features that will develop later.

Carroll reproduces beautiful photographs of fly embryos showing (by means of technical manipulation) brightly colored regions, where each region — blue, green, red, yellow — corresponds to the activity of a particular collection of genes. A couple of hours after fertilization, the oblong embryo is about one hundred cells in length from end to end (or from “west” to “east”, as the researchers prefer to say, with west corresponding to the future head pole). Thanks to the differentiated activity of tool kit genes, the western, middle, and eastern sections of the embryo clearly reveal themselves as separate bands.

As these bands fade, they are replaced by seven stripes over the eastern two-thirds of the embryo. Each stripe, together with the neighboring darker band, marks out a pair of future segments of the fly larva. Then these stripes, too, under the influence of yet another group of genes, give way to fourteen stripes indicating the fourteen segments of the larva individually. Most of these latter stripes persist throughout development, and they lead rapidly to actual segmentation of the embryo.

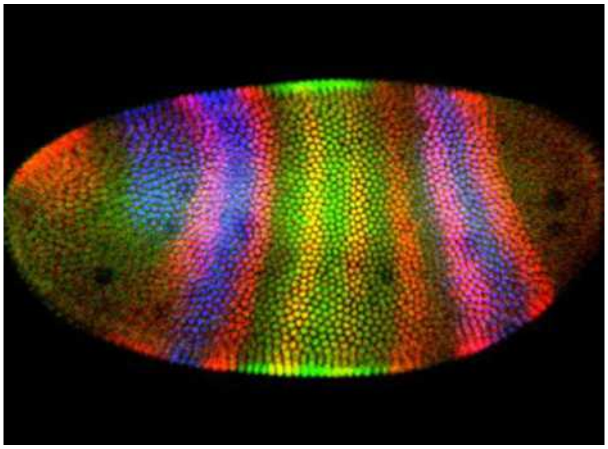

Figure 11.3. Artificially colored bands on a fruit fly embryo, showing the location of particular proteins, which in turn result from differential gene expression and signal the future location of fly segments.

The photographs are spectacular, and leave no doubt in one’s mind that the early embryo, uniform and undistinguished as it might appear under ordinary light, is in fact an embodiment of order and form. There is a head and tail, with degrees of longitude between them, and likewise a top and bottom (dorsal and ventral regions), with degrees of latitude. And different “modules” (as Carroll calls them) are already marked out for the development of specific organs and appendages.

Carroll’s own work has focused on butterflies. Here again the design to come is signaled by the distribution of tool kit proteins. Carroll produces photographs showing these proteins in the developing wing, occupying exactly those locations where the beautifully decorative spots and stripes and rings will eventually appear. *It's as if the future design were in some way already there.*

The mastery of genetic switches

But tool kit genes are only part of the picture. It's true that the protein bands in the early embryo are associated with genes that are activated in those bands so as to produce ("express") the proteins. Certain genes that are "on" or "off" within the band, will be in the opposite state outside the band. But what is supposed to coordinate this activation and deactivation of genes?

Carroll's answer is at the same time his central theme: the tool kit genes are systematically turned on and off by a computer-like "operating system" — a vast network of switches residing in those portions of DNA that do not "code" for proteins. Acting, according to Carroll, like a global positioning system (GPS), these switches "integrate positional information in the embryo with respect to longitude, latitude, altitude, and depth, and then dictate the places where genes are turned on and off".

Each switch, as Carroll describes it, is actually a short stretch of DNA controlling a particular tool kit gene. Often there are multiple switches controlling a single gene. Proteins (produced by yet other tool kit genes) can bind to these switches, altering their state. The overall pattern of switch states for a particular gene then determines whether that gene will be activated or repressed. This allows a single gene to be used in many different ways at different times and places — for example, in the development of our own heart, eyes, and fingers. Everything depends on the states of its associated switches. "The entire show", writes Carroll, "involves tens of thousands of switches being thrown in sequence and in parallel" (p. 114).

The governing image in all this is that of the computer. He refers to DNA switches as "fantastic devices [that] translate embryo geography into genetic instructions for making three-dimensional form" (p. 111). The computational powers of the controlling network of switches, he tells us, allow fine-grained management of the expression of individual genes. But at the same time the switches are the key to a software-like modularization of the organism, making it possible for entire features (a spot on a wing, an insect's eye, a digit on a mammal's foot) to come or go — or be modified in dramatic ways — with the flip of a few switches.

Can we trace form to something other than form?

All this raises an obvious question, which, in a way, Carroll himself acknowledges. Suppose we have a fly embryo divided into three regions marked out by proteins A, B, and C.

> You might ask, where do these patterns of tool kit proteins A, B, and C come from? Good question. These patterns are themselves controlled by switches in [the associated] genes *A*, *B*, and *C*, respectively, that integrate inputs from other tool kit proteins acting a bit earlier in the embryo. And where do those inputs come from? Still earlier-acting inputs. I know this is beginning to sound like the old chicken-and-the-egg riddle. Ultimately, the beginning of spatial information in the embryo often traces back to asymmetrically distributed molecules

> deposited in the egg during its production in the ovary that initiate the formation of the two main axes of the embryo … I'm not going to trace these steps — the important point to know is that the throwing of every switch is set up by preceding events, and that a switch, by turning on its gene in a new pattern, in turn sets up the next set of patterns and events in development. (p. 116)

Here, then, is the general thrust of Carroll's attempt to elaborate "the simple rules that shape animal form". But perhaps we may be forgiven a certain unease at this point — a discomfort, to begin with, about a claim of simplicity applied to "tens of thousands of switches being thrown in sequence and in parallel". Before we can see the exquisitely detailed and aesthetically satisfying spatial pattern of pigments on the butterfly's wings (or the peacock's feathers), there must be a correspondingly exquisite and detailed pattern of flipped genetic switches. The one form must in some way be foreshadowed by the other.

It is no wonder that Carroll says "I'm not going to trace these steps". For if the important fact "is that the throwing of every switch is set up by preceding events", then it appears that the tracing would not give us an *explanation* for the form of development of an organism — not in the usual causal sense of "explanation". It would simply (and worthily) trace the form through successive manifestations, one snapshot of which might be given in an image such as that of the fruit fly embryo's colored bands.

The problem with the usual sort of causal explanation is that, as we saw in Chapter 7 and will see much more fully in Chapter 14, "causal factors" isolated from studies of gene expression end up converging upon each other and extending throughout the entire cell and organism.

So we might wonder whether the effort to define unambiguous causes always resists a final resolution in terms other than those of form — that is, resists our attempts to *explain* form. Perhaps we can only *illustrate* it.

Bothersome, too, is the casual assumption that something in fluid, ever-transforming cells (and in groups of cells, and in the organism as a whole) operates in meaningful analogy to a computer's precisely machined, rigidly fixed, transistor-based, engineer-designed hardware. No specific support is offered for this critical and wholly improbable fundament of Carroll's argument.

Moreover, we do know that his language at this point is misdirected. He speaks as if particular switches "control" genes or "dictate" such-and-such an outcome. But, as we saw in Chapter 9 ("A Mess of Causes"), such straightforward, machine-like causes are foreign to the life of organisms. The endlessly expanding sciences of genetics and epigenetics, as we saw in Chapter 7 ("Epigenetics: A Brief Introduction") and will see much more fully in Chapter 14, ("How Our Genes Come to Expression") have shown us that influences flow toward genes from just about every corner of the cell and organism — and they do so as all those corners are themselves caught up in the overall developmental transformation of the whole organism. Contrary to any picture of neat controlling causes, we are forced to understand the entire organism as itself the fundamental, rock-bottom, metamorphosing "cause" of its own development. (See also Chapter 10, "What Is the Problem of Form?")

Discomfort also arises when we contemplate Carroll's ever-receding series of "inputs" that, as we look further and further into the past, finally peters out in the vagueness of “asymmetrically distributed molecules” in the earliest stages of an egg’s development.[2] Such vagueness at the decisive beginning of the entire developmental process, when all the organism’s still-to-unfold features lie potent in the egg, does not say much for our present understanding of the supposedly “simple rules” that explain the observed complexity and seamless unity of every unique life form.

So, then, returning to our central question: where in the entire developmental sequence can we honestly say, “Here we are *explaining* the form itself, as opposed to simply describing a continuous manifestation and transfiguration of form?”

If the arrangement of an insect’s body segments is prefigured by various patterns of protein deposition, and if the protein patterns are prefigured by patterns of gene expression, and if the patterns of gene expression are prefigured by precisely arranged spatial patterns of switches being turned on and off, then we may be describing a play of form over time and at different levels of observation, from the molecular level to that of the whole body part. But if we try to see this as an explanation of how significant form arises from the unformed, we can hardly help noticing that we have merely pushed the problem of form backward in time and downward in scale, until it vanishes from sight, still unexplained.

Endless transformations most beautiful

All processes of development and growth are *metamorphoses*. If we were able to view a three-dimensional movie showing the magnified interior of our developing bodies, the significance of the proceedings would be overwhelming. We would watch a single zygotic cell reproduce and diversify, yielding eventually a trillion or more cells proceeding along hundreds or thousands of distinct trajectories of differentiation.

It would almost be as if we were watching a vast menagerie of wildly different, micro-sized organisms, multiplying, writhing, dancing, and contorting themselves in different rhythms and patterns in countless niches or compartments throughout all the tissues and organs of the body. Each of those “organisms” has its own intricate form, changing from cell generation to cell generation, and yet it all happens under the “discipline” of the larger and unfathomably complex, developing form of the whole organism.

Every organ would have its own distinct story to tell. In our developing brains, for example, we would see not only the differentiation of the many unique cellular lineages in that organ, but also the forming of significant functional connections and patterns of interaction as the brain shaped itself (or was shaped) to the form of our cognitive experience and motor activity. The lungs would likewise be shaped for and by the air and our eyes for and by the light, just as our bones are shaped for mobile support under the influence of gravity and our habits of movement.

And, of course, the picture is just as lively and striking when we step back and look at any organism as a whole. Here is the well-known description by Thomas Huxley, Darwin’s pre-eminent apologist during the latter part of the nineteenth century:

> Examine the recently laid egg of some common animal, such as a salamander or newt. It is a minute spheroid in which the best microscope will reveal nothing but a structureless sac, enclosing a glairy fluid, holding granules in suspension. But strange possibilities lie dormant in that semi-fluid globule. Let a moderate supply of warmth reach its watery cradle, and the plastic matter undergoes changes so rapid, yet so steady and purpose-like in their succession, that one can only compare them to those operated by a skilled modeller upon a formless lump of clay. As with an invisible trowel, the mass is divided and subdivided into smaller and smaller portions, until it is reduced to an aggregation of granules not too large to build withal the finest fabrics of the nascent organism. And, then, it is as if a delicate finger traced out the line to be occupied by the spinal column, and moulded the contour of the body; pinching up the head at one end, the tail at the other, and fashioning flank and limb into due salamandrine proportions, in so artistic a way, that, after watching the process hour by hour, one is almost involuntarily possessed by the notion, that some more subtle aid to vision than an achromatic, would show the hidden artist, with his plan before him, striving with skillful manipulation to perfect his work[3] (Huxley 1860).

Do we really need some still more subtle instrument that will reveal a hidden artist working from outside — which, of course, Huxley didn’t believe in — or do we need rather to credit the capacity of our own, educated eyes to see, as Huxley did, the *inherent artistry* that informs the processes right there in front of us? The embryo plainly and objectively manifests a power of unified expression, of metamorphosing organic form — something a child can recognize. Why should we not accept this power exactly as and where we observe it — as a living *power* — just as we accept the very different power of gravity in exactly the terms of *its* manifestations?

And, despite Huxley’s reference to “a formless lump of clay”, never in all this drama of transfiguration do we witness a cell or any other element being constructed from formless substance (if such substance could even be imagined) — or being built from preexisting, “plug-and-play” parts. The parts undergo transformation simultaneously with the whole, and only as expressions of the whole.

The starting point of it all is the living zygote, and in its flourishing and wonderfully structured context-embeddedness, its life “overflows” and multiplies. The zygote’s original, one-celled unity is never lost, but rather is subdivided and differentiated. It is worked on from within and influenced from without (that is, from the environment), according to the unfolding of its governing principles of form.

These principles — those of the type, or species — are regarded by every embryologist as telling *one, unified story* from zygote to maturity and senescence. Further, the informing power that is characteristic of that story remains “in force”, as far as circumstances allow, regardless of drastically different nurturing environments, and even in the face of disfiguring insults inflicted by laboratory technicians. The organism responds to every insult by bending it, as far as possible, toward the normal pattern of development.

The existence of this governing pattern, or form, in every different sort of organism is a decisive truth of biology. No matter how far down toward the molecular we go in trying to explain form, we find our explanations themselves to be always based on considerations of form. We never seem able to get beneath or behind these considerations so as to grasp something more fundamentally explanatory than form itself.

Even the classic efforts to explain everything based on genes has now become ever more vividly an elucidation of form — form that is already in play at the level of genes and chromosomes. For example, some geneticists speak of "genomic origami", while others refer to the three-dimensional "dance" of chromosomes in the nucleus — a spatially significant performance essential to the expression of the right genes in the right amounts at the right times (Chapter 3).

This is a good place to return to the wisdom of the twentieth-century cell biologist, Paul Weiss, who once remarked:

> There would be less room for misconception if instead of referring to developmental dynamics as "formative", we were to designate them as "transformative", for then the notion that order or organization as such are created *de novo* [anew] within a totally random pool of unit elements could not arise (Paul Weiss 1971, p. 39).

We are always watching the transfiguration of existing form — a re-shaping that can be seen as a further development of the form already there and, at the same time, as an active movement toward a more fully realized form yet to be achieved. Existing material resources or obstacles may support and constrain the ongoing metamorphoses, but they do not determine its forward direction. The determination is found in the principles of form governing the particular biological kind. The physical *manifestations* of this metamorphosis are no more *explanations* of it than the physical planets — conceived apart from the ideal, mathematical lawfulness expressed through them — explain the form of the solar system.

And this can remind us that all physical interactions of matter — even the inanimate interactions often considered most basic or fundamental — already express principles of form represented by a governing lawfulness. But when we look at an organism we discover additional principles of form superimposed on those shaping inanimate nature. That is, we always find ourselves watching how physical processes are not merely physical processes, but rather are actively enlisted, adjusted, and coordinated in the face of differing circumstances — coordinated according to a more or less centered agency and a distinctive sort of lawfulness through which we see progressively realized a specific way of being, the characteristic form of an organism's kind.

What then is form, and why can't we explain it?

I mentioned above how Sean Carroll, when trying to explain form, found himself tracking form backward and downward until it vanished from sight in the presumed asymmetric arrangement of molecules within an egg cell. These "primordial" molecules in the scarcely structured egg hardly seem the ultimate, revelatory basis for explaining the not yet realized form of the mature organism. So what is the explanation Carroll claims to possess? There doesn't seem to be any explanation until we can see, as in Figure 11.3, the first well-formed structures we can relate to later well-formed structures.

Figure 11.4. The moth, *Automeris janus*, illustrated by George Shaw (1751-1813) in *The Naturalist's Miscellany*.

So we can hardly help asking, "What if the real problem is that the causes Carroll was looking for — mechanistic causes of form — simply don't exist?" Maybe we never are, at any stage of our investigation, tracing physical mechanisms that *explain* observed form. Maybe apprehending form in its own terms — and doing so as perceptively as possible — is how we make sense of biological phenomena. Maybe a playing of form is what every material phenomenon in general and every biological phenomenon in particular just *is* most essentially.

The word "form" has a strikingly wide range of uses. We can, of course, talk about form in the static sense of "spatial arrangement of parts". But we can also talk about the form of a ritual, ceremony, or other procedure; the expressive or aesthetic form of a great painting; a form of logic; a form of behavior; or "good" and "bad" form in relation to some standard of performance.

What is common to all these usages is one or another sort of conceptually graspable order. Through this order we apprehend at least part of the *meaning* of whatever is going on. To see the form of anything at all is to see significant connections and relations — what it is that makes something into a *this* rather than a *that*, a redwood rather than a willow, a squirrel rather than a rat, a virtuous act rather than an ugly one.

But the phrase "conceptual order", as heard by modern ears, is far too anemic. Speaking out of the past, Samuel Taylor Coleridge offered us a useful corrective. Owen Barfield, in explicating Coleridge's thought, ascribed to the late eighteenth and early nineteenth-century poet and philosopher the belief that a true physical idea "*is* at the same time a law of nature" — it is "nature behaving". For example (regarding gravity), Coleridge held that "the very law [idea] itself is also the power" (Barfield 1971, p. 126).

The form of a thing is not just another thing added to the first. It belongs to the thought-aspect through which the thing gains a muscular power to become *this sort of appearance* and not *that sort*.

This brings us to the underlying difficulty that Carroll (and biologists generally) run up against. Their physical world has been denuded of its thought-aspect. It has, in the style of nineteenth-century classical physics, finally been reduced to inertly mindless, and therefore qualityless, particles. These particles can have nothing to do with the reality of inherently qualitative form. And so, as we have seen with Carroll's non-explanatory explanations, the only real understanding slips in along with the illicit visions of form that are allowed to "contaminate" (or unconsciously enflesh) the picture of genetic particles and computer switches.

So let’s be clear about the thought-full reality of form

And so we have our conclusion: the reason why attempts to explain form never seem to get beneath the reality of form is that our elucidation of the various sorts of organismal form is itself a great part of the understanding we seek. The aim of biology, after all, is to grasp the governing ideas of the organism. We achieve a good part of this aim when we recognize the whole organism as a being of significant form.

This may seem an anemic conclusion to conventionally minded biologists. But that is because we still need to illustrate as vividly as possible what it means to gain a profound grasp of an organism’s form, and also because we need a reckoning with the *causal* role of form. These topics will be taken up in Chapter 12.

Further, none of this is to say that we should refuse to interest ourselves also in the chemistry and physics of organisms. That may indeed become our consuming passion. But chemistry and physics are not biology, and the ideas that are physical laws have nothing in themselves to explain the ideas of biological form. This is why Carroll goes around in circles when he claims to have such an explanation.

It is not that biologists *altogether* miss the thought-aspect of form. It’s just that they see it half-consciously, at best, and in a terribly distorted fashion, due to reliance upon mechanistic imagery. Carroll illustrates this when he, like so many other biologists, adopts the computational point of view with unquestioning enthusiasm. In this way he imports into the genes of his butterflies whatever useful programmatic thoughts and intentions he requires — thoughts and intentions just like those that have so carefully been imprinted by engineers upon the structure of programmed devices. He does this without explicitly acknowledging either his reliance upon those thoughts and intentions, or their severe incompatibility with the workings of the wisdom embodied in the simplest of organisms.

And so he tells us that tool kit genes “know” when to act, and that “operating instructions” are embedded throughout the genome in networks of genetic switches. By virtue of their finely detailed control, constellations of these logic switches “encode” the anatomy of animal bodies. Summarizing his understanding of all those thousands of switches, he writes:

> Part genetic computer, part artist, these fantastic devices translate embryo geography into genetic instructions for making three-dimensional form (pp. 110-11).

“Fantastic” devices, yes — too fantastic, in fact, to exist as *devices* rather than as an activity of living beings.

Apparently Carroll, and all the other biologists who in one way or another employ the same language, have come to the (perhaps unconscious) conclusion that we really do need to find Huxley’s “invisible artist” — but that we must do so mechanistically, re-imagining the artist as a designer-engineer. It somehow seems too distasteful to take seriously the artistry we can observe actively at work in the organism itself.

Where are we now?

Is Form a Primary and Irreducible Feature of the Organism?

In the chapter introduction, I asked where we might glimpse the global, coordinating power that guarantees the infinitely detailed and aesthetically satisfying form of organisms — for example, the pattern of color in a duck's speculum — given that physical laws by themselves know nothing of the sustained coordination required.

In both Chapter 10 ("What Is the Problem of Form?") and this one I have argued that mechanisms do not give us workable models for the play of form in organisms. In this chapter I have suggested further that the attempt to explain form seems misconceived in the first place, since we can never get "behind" form to an explanatory principle more basic. I have also pointed out that an appeal to form is usually an appeal to some part of the qualitative thinking through which we discover a phenomenon to be understandable.

If the effort to explain form is misdirected, does this mean that the idea of explanatory causes has no place in our understanding of biological form? Not at all. Maybe we will be reminded here of the fact that *formal causes* have long been recognized as essential for our understanding, going back to Aristotle. Perhaps the apprehension of principles of form yields understanding precisely because they themselves are principles of causation, although in a crucial sense differing from our usual understanding of causes.

In the next chapter we will look at three research efforts aimed at elucidating form in the phenomena of life. These efforts are irreducibly qualitative, and in their light we can understand that form is not so much a result of causes (as causes are commonly understood in biology), but rather is itself a kind of cause.

Notes

1. Figure 11.2 credits (left): Krista Lundgren, United States Fish and Wildlife Service; (right): The Feather Factory, https://thefeatherfactory.co.uk.

2. The origin of this asymmetry is often assigned by biologists to the "random movements" of some number of molecules. But such randomness does not contribute much, if anything, to the sort of scientific understanding we seek. If we consider the eggs, or germ cells, of species with radically different forms — say, anteaters and eagles — random movements in the developing germ cells do not help to explain the specific and differing character of those forms.

3. This, quite evidently, was written during a period of much greater intellectual freedom and honesty than we see today — that is, before the veil of blindsight began to hinder the eyes of biologists, preventing them from explicitly acknowledging, or even being conscious of, the

purposive dimensions of organic activity. It is worth asking: What is the fear underlying this blindsight?

Today it certainly seems that, at least in part, it is fear of what intelligent design [ID] advocates might do with “injudicious” language about purpose and design. And what makes the situation so difficult is the fact that ID so closely reflects conventional biology. In the battle between ID proponents and establishment biologists, it is very hard for the antagonists to distinguish themselves from each other. There is, above all, the mutual insistence by both sides that organisms are machine-like. Machines, of course, are designed entities — designed from without by humans. So conventional biologists have the “devil” of a time distinguishing their version of science from that of ID theories holding that organisms are designed from without by some supernatural power.

The argument over ID is easily resolved through scientific observation — by showing that both sides are wrong in conceiving the organism mechanistically (a project to which I have tried to contribute in this book). The essential question is the following (as I put it in Chapter 10): Do organisms show evidence of being designed and tinkered with from without, or are they enlivened from within? The fact is that we never see a designing power or force that acts other than through what appears to be the living agency of the organism itself. Or, as philosopher Ronald Brady has put it: “We cannot detect, in [organic] phenomena, the distinction between ‘that which is to be vitalized’ and ‘that which vitalizes’” (Brady 1987).

And so, despite common assumption, the argument between the two camps has no bearing on the tenets of true religion. I know of no religion that does not view divine power, such as it may be, as immanent in the world as well as transcendent — at least, no religion that I can easily imagine a spiritually minded person today being tempted to profess. The reigning conviction of machine-like design in biology is a conviction governed by materialist and anthropomorphic thought, whether it is pro- or anti-intelligent design. This thought is capable of conceiving organisms only as if they were built up through a human-like process of manufacture — an external assembly of discrete and unliving physical parts — rather than growing by means of a living power within.

Sources

Barfield, Owen (1971). *What Coleridge Thought*. Middletown CT: Wesleyan University Press.

Brady, Ronald H. (1987). “Form and Cause in Goethe’s Morphology”, in *Goethe and the Sciences: A Reappraisal*, edited by F. Amrine, F. J. Zucker, and H. Wheeler, pp. 257-300. Dordrecht, Holland: D. Reidel. Available at https://www.natureinstitute.org/ronald-h-brady/form-and-cause-in-goethes-morphology

Carroll, Sean B. (2005). *Endless Forms Most Beautiful: The New Science of Evo Devo*. New York: W. W. Norton.

Darwin, Charles (1859). *The Origin of Species*. Available online at https://archive.org/details/DarwinCharlesTheOriginOfSpeciesEN1859467P./

Darwin, Charles (1860). Letter to Asa Gray (April 3). Available at https://www.darwinproject.ac.uk/letter/DCP-LETT-2743.xml

Hoffmann, Banesh (1959). *The Strange Story of the Quantum*, second edition. New York: Dover.

Huxley, T. H. (1860). *The Origin of Species*, Collected Essays vol. II. Available online: https://mathcs.clarku.edu/huxley/CE2/OrS.html

Portmann, Adolf (1967). *Animal Forms and Patterns: A Study of the Appearance of Animals*, translated by Hella Czech. New York: Schocken Books. Originally published in 1952.

Weiss, Paul A. (1971). “The Basic Concept of Hierarchic Systems”, in *Hierarchically Organized Systems in Theory and Practice* by Paul A. Weiss, H. K. Buechner, J. S. Coleman et al., pp. 1-43. New York: Hafner.

Chapter 12

Is a Qualitative Biology Possible?

The philosopher, Ronald Brady, once wrote about his undergraduate experience this way:

> When I began college as a chemistry major my enthusiasm for science was somewhat dampened by meeting a professor of chemistry who pointed out the difference between my own goals and those he, as an experienced professional, would call mature. My passion, he noted, was entirely focused on direct experience — my sense of chemical change was invested in sensible qualities: in smells, colors, the effervescence of liquids, the appearance of precipitates, the light and violence of flame, etc. But, he countered, this was probably closer to medieval alchemy than to chemistry. The latter is really a matter of molecular and atomic events of which we can have only a theoretical grasp, and the sensible experience on which my excitement centered was secondary ... I was reminded of him when I spoke to a morphologist at Berkeley about my interest in Goethe's attempt to approach science by keeping to direct experience. The morphologist responded: "You are interested in this approach because you are a Nature appreciator, while I am a productive scientist." It is always nice to see where one stands.[1]

Ever since the Scientific Revolution, physical scientists have held to the conviction that, whereas nature speaks decisively in the language of mathematics, the qualities of nature are not actually qualities *of nature*, but rather additions provided "from outside" by human subjectivity. And where physical scientists have led, biologists have done their best to follow.

If, as is commonly thought, qualities reside outside the bounds of any rigorous science, including biological science, then the very idea of a qualitative biology is self-contradictory. There can be no such science. Since this entire book is founded on the contrary assumption — an assumption explicitly defended in Chapters 13 and 24 — it feels obligatory to provide some particularly instructive examples of what a qualitative biology might look like.

In what follows I offer three such examples of widely differing sorts. The first involves the study of a single animal, the second a study of leaf sequences on certain plants, and the third a study of systemic morphological, behavioral, and other patterns recognizable in evolved groups of organisms, yet inexplicable in terms of present evolutionary theory.

An animal expressing the character of the tropical forest

Craig Holdrege is a biologist with a predilection for what he calls “whole-organism studies”. In his research he struggles to arrive at a unified picture of an organism by approaching it from all sides: morphological, physiological, behavioral, ecological, and more. The knowledge he arrives at in this way is irreducibly qualitative. But what does that mean? Before we look at Holdrege’s sketch of the three-toed sloth, let’s take in some basic information about this creature of the South American rain forest:

- The sloth spends much of its active life clinging to or hanging from the branches of trees. It sleeps or remains inactive for the greater part of every day.
- The sloth has proportionately less muscle mass than most mammals. It also has a higher percentage of retractor (pulling) muscles, and its muscles react more slowly than those of other mammals.
- The sloth makes use of smelling more than seeing or hearing.
- Its body temperature varies more with the ambient temperature than in most other mammals.
- The fur coat of the sloth is often covered with algae. Also, beetles, moths, and various other insects, as well as mites, may inhabit the fur, sometimes with the individuals of a particular insect species numbering a hundred or more.
- Gestation period: four to six months.
- Teeth: continually growing; not pre-formed, but shaped by use.
- Eyes: can retract into their sockets.
- The sloth descends from the trees to the ground about once per week to defecate. Its feces are only slightly decomposed after six months. In defecating and urinating, the animal may lose more than a quarter of its bodily weight.
- The sloth is relatively non-reactive to pain and injury.

There you have a collection of facts about the sloth. But you hardly have a coherent *picture* of the sloth. Based on these facts, viewed in mutual isolation, you can say little about the distinctive *qualities* of the animal. But now let me briefly summarize a part of Holdrege’s discussion of the sloth as a “whole organism”. (The balance of this section is drawn from Holdrege 2021.)

What first of all strikes one about the sloth is, of course, its “slothfulness”. It is indeed a slow creature, spending the greater part of the day sleeping or otherwise inactive. It will sometimes cling so stubbornly to a given position that a tree limb must be sawed off in order to remove it. When it does move of its own accord, it pulls itself slowly along the tree branches from which it hangs "by all fours", drawing leaves to its mouth with its front limbs and eating them. When it descends from the tree to urinate and defecate on the ground, the process is so deliberate and gradual that the wingless moths who have taken up residence in the sloth's fur have plenty of time to crawl off the animal, lay their eggs in the fresh dung, and return to their furry habitat.

But "slothfulness" is much more than mere speed of movement. It qualifies every aspect of the animal. For example, the sloth's digestive processes, about which its life seems to be centered, are remarkably slow. According to one researcher, "after three or six days of fasting, the stomach is found to be only slightly less full". The stomach is four-chambered like the cow's, but digestion takes about ten times longer than in the cow.

With its reduced muscle mass, the sloth generally performs about ten percent of the physiological work typical of similar-sized mammals. "All metabolic processes are markedly measured in tempo. Sloths use little oxygen, breathe slowly, and the respiratory surface of their lungs is small". Further, a four-to-six-month gestation period compares to a little over two months for the similar-sized cat. And even the sloth's dung may be only slightly decomposed after six months — this amid the intense decompositional processes of the rain forest. This is thought to help slow down the high nutrient recycling rates for certain trees, helping to stabilize some components of the ecosystem. In sum,

Figure 12.1. A three-toed sloth flowing up a tree limb.[2]

> The sloth brings slowness into the world. This is not only true of its reactions, movements and digestion. It also develops slowly in the womb and has a long life span for a mammal of its size.

Clearly the sloth is not a creature of rapid or pronounced change. In this it expresses features of its environment. The tropical rain forest is a place of great constancy — days of equal length throughout the year, the air warm and humid with little seasonal variation, the light levels always low beneath the dense forest canopy, afternoon rains every day.

> The uniformity of light, warmth, and moisture — in intensity and rhythm — mark the rain forest. And it is hard to imagine a rain forest dweller that embodies this quality of constancy more than the sloth. From meters below, the sloth is sometimes described as looking like a clump of decomposing leaves or a lichen-colored bough.

But there are many ways an animal can reflect its environment. The sloth exhibits a certain passive, yielding character so that it is, in a sense, “formed from the outside”. For example, in a way that is extremely unusual for warm-blooded animals, the sloth’s internal temperature varies considerably — and does so less in accord with its own activity than with the ambient temperature. (Unlike other mammals, the sloth cannot actively raise its temperature through the muscular activity of shivering.)

Similarly, the sloth does not so much overcome gravity as yield to it. With its skeletal structure loose and flexible rather than fixed, and with retractor (pulling) muscles dominant, it lacks the ability to push against gravity and raise itself up. Placed upright on a smooth, flat surface, its legs will splay out and it will be helpless to move unless it can find toeholds (clawholds) for pulling itself along. (See figure below.) It spends much of its life either curled up in a ball or hanging by its hook-like claws from tree branches.

In maintaining the balance of its life, the sloth does not strongly counter external forces and conditions with its own activity.

This, perhaps, makes it less surprising that the sloth is so oddly nonreactive to experiences of pain or injury. Pain occurs where the boundary between self and world is violated, but the sloth seems to have no vivid sense of this boundary. It will cling stubbornly to the very object that is injuring it. One researcher who kept sloths in his home tells of an animal burning and smoking as it sat on a light bulb in a lamp. But upon being rescued, it only protested and tried to cling to the lamp. Another researcher describes a sloth that acted “normally for a long time after it had received a wound which practically destroyed the heart“. As part of its receptivity to the world, the sloth (Holdrege writes) “seems not to live as intensely in its body as other mammals, being quite insensitive to pain”.

Figure 12.2. A three-toed sloth trying to cross a road. Sloths are rather helpless on a flat surface unless they can find toeholds to pull themselves along.[3]

Even in its digestion the sloth shows its passive and nonreactive character. Although its stomach is four-chambered like the cow's, this stomach "is more like a vessel that needs to remain full than a place of intensive muscular activity, secretion, mixing and breaking down, as it is in the cow". Or, again, the sloth's teeth are not pre-formed with crown cusps and ridges as in other mammals (and especially grazers); rather, they emerge as simple cones and are shaped through their engagement with food. In this sense, the sloth's teeth are formed from the outside.

So we see that in many ways the sloth does not so much respond to the rain forest environment as receive its imprint. Even the sloth's fur, which soaks up water "like a sponge", is often green-tinted from the growth of algae. So it assumes some of the appearance and character of its surroundings. And this fur provides a little rain forest habitat of its own, being the home, as we have noted, for numerous beetles, moths, and other insects, as well as mites.

Like most mammals, sloths do occasionally groom themselves. But, as one pair of researchers reports, the grooming effort is so sluggish that moths "may be seen to advance in a wave in front of the moving claws of the forefoot, disturbed, but by no means dislodged from the host".

Fully consistent with this image of an animal that receives the environment into itself rather than actively projecting itself outward, Holdrege recognizes in the sloth "a primary gesture ... of pulling in or retracting". We have already noted the predominance of retractor muscles along with the manner in which the sloth pulls itself along a branch and brings leaves to its mouth. The head itself is a picture of this withdrawn and in-drawing manner of being. Lacking the protruding snout of most grazers, the skull is extraordinarily round and the head is not clearly separated from the rest of the body. The sloth's ears are tiny and do not project out into the environment. Its eyes can retract into their sockets. Both sight and hearing are, in the sloth, quite weak; smell — the one sense whereby part of the environment is drawn deeply into the organism — is the primary sense. Imagine yourself living in a world of wafting smells: no distinct boundary between self and other is given through this sense.

Slowness and constancy; receptive openness to the environment; a passive, somewhat withdrawn character; a gesture of pulling in or retracting rather than projecting outward; being formed from the outside — each of these phrases emphasizes a slightly different side of a unitary way of being. We can, with inner effort, bring all the sloth's traits into a coherent picture that holds together. And when we do this, claims Holdrege, we find that "every detail can begin to speak 'sloth'". That is, we can recognize a quality of "slothness" that shines through all the details and makes them into a single, expressive whole.

Of course, Holdrege's own description is much more organic than this haphazard, fragmented, and incomplete summary. But, in comparing the list of facts offered at the beginning of this section with the attempt to weave these facts into at least the bare beginning of a connected fabric, perhaps you can begin to glimpse the meaningful unity that a qualitative approach to the sloth might make available. The qualities are, so to speak, recognized *between* the isolated facts. Only by virtue of this bridging function of qualities through which diverse features are seen in a common light can we apprehend the unity of an organism.

It is impossible to comprehend this unity when we approach an organism in the usual terms of evolution and natural selection — that is, when we approach it as a collection of independently arising traits, each of which offers its own selective advantage. There is no principle of unity here. We see the unity only in terms of the organism itself, viewed as a whole, expressing itself out of its own nature. And if typical evolutionary explanations give us no approach to this readily observable unity, then clearly something fundamental is missing from our evolutionary understanding.

The problem of organic form

Johann Wolfgang von Goethe (1749-1832), who pioneered morphological studies (and gave us the word "morphology"), wanted his readers to understand about the new science that "its intention is to portray rather than explain". At the same time, however — and rather mysteriously for most modern ears — he emphasized that the portrayal was itself all the explanation we needed: "Everything in the realm of fact is already theory … Let us not seek for something behind the phenomena — they themselves are the theory".[4]

This is the puzzle that the philosopher Ronald Brady undertook to elucidate in one of the most important (and most widely unread) papers of the twentieth century: "Form and Cause in Goethe's Morphology" (Brady 1987):

> Any modern reading of Goethe's morphological writings must struggle with the author's apparent satisfaction that his "morphology" … was both a descriptive science and a causal one. This unlikely attitude is made all the more difficult by Goethe's suggestion that form — at least in the sense of "archetypal" form — is itself causal … I shall argue in this paper that Goethe's notion of archetypal form represents an important advance in the phenomenology of organic form, and that it does indeed have causal implications.

(All quotes will be from Brady's paper unless otherwise indicated.)

We are assessing form when we judge, for example, whether two trees — one short, thin, and spindly, growing at the alpine tree-line, and one tall and lush, growing at sea level — are both Norway spruce. Likewise, we are assessing form when we ask whether the human arm is *homologous* with the fin of a whale and wing of a bird. That is, can we say that arm, fin, and wing are in some sense the *same* limb, whatever transformations may have differentiated one from another? And a similar question arises when we consider the succession of vertebrae along the spine of a human being or other vertebrate. Can they be seen as variations of a single design?

In studying plants during the later eighteenth century, Goethe recognized a commonality uniting such diverse features as the seed leaves, foliage leaves, sepals, petals, pistils, and so on. All these organs in any particular plant, he claimed, are transformations of a single archetypal form, a form he chose to call the *leaf*. The foliage leaves are just one set of embodiments of this archetypal *leaf*. But while the validity of Goethe's discovery has been widely accepted within biology, the nature of that discovery, according to Brady, has been just as widely misinterpreted.

Figure 12.3. Leaf sequence of common groundsel (*Senecio vulgaris*). The figure shows all the foliage leaves of the main stem of a single plant from bottom to top (in the figure from left to right). The first (at left) is one of the two cotyledons of the plant. The sequence is otherwise complete; no leaf is missing.[5]

Goethe was not simply abstracting a set of common features from a diverse set of forms, yielding a fixed schema. No such schema can make sense of the processes of becoming we observe, for example, in the leaves appearing in sequence along the stem of a plant that grows anew from ground level every year (whether as an annual or perennial — see Figure 12.3):

> Goethe's common organ, or *leaf*, is not a simplification of foliar members. All empirical forms are, for him, equally particularized, and his general organ can be general only by lacking such particularity. His *leaf* accomplishes this requirement *by having no form at all*.

In other words (as we will see), the archetypal leaf of the plant has no form in the usual sense — no *static* material form — but rather is a special dynamic sort of form that is *generative* of particular, sensible forms. We recognize it as a formative power or potential. This is where *something like* causation (for which there is no clear concept in modern science) enters the picture, and it is also where the modern reader stumbles. However, Brady takes great pains to make the point accessible. We will follow his line of thought in some detail.

How to generalize upon a transformational series

The figure below shows, from bottom-left and clockwise around the circle to bottom-right, a sequence of leaves taken in ascending order along the stem of a single meadow buttercup (*Ranunculus acris*). For pedagogical purposes the figure is somewhat simplified, with some leaves omitted. Also, in the first few leaves only part of the leaf stalk is shown.

You will note that the attempt to abstract what is common from all the leaves might yield something more or less like the simple form at the end of the clockwise movement (bottom-right).

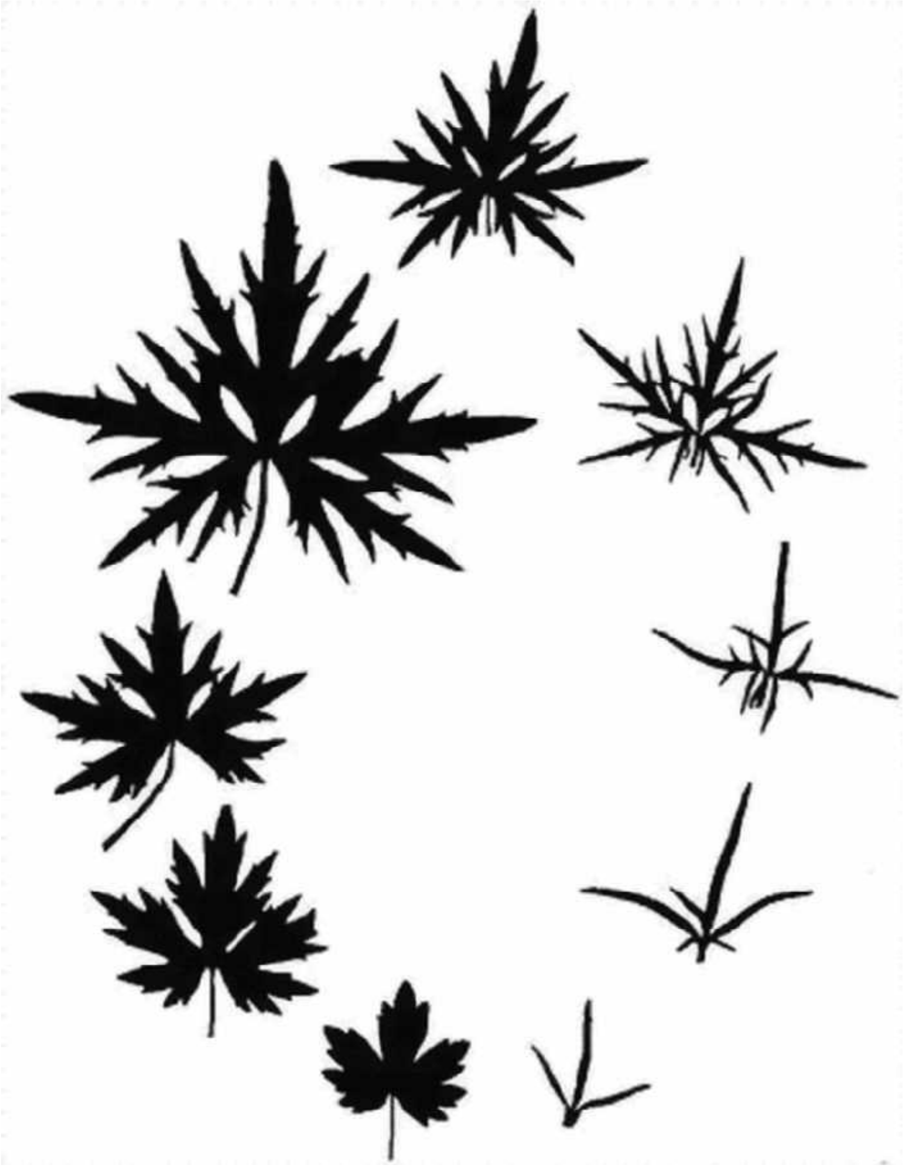

Figure 12.4. A leaf sequence from a buttercup plant (*Ranunculus acris*). See text.

But suppose we declared this one leaf to be the “Gestalt” underlying all the leaves in the sequence. This would be of no value, because the simplified leaf, from which so much detail has been removed, fails to provide a principle for recognizing the fit (or lack of fit) of the other forms — or of any new leaves we might be shown. We can imagine countless different ways for a leaf to be tripartite without at all conforming to the pattern that distinguishes *Ranunculus acris* from other species.

No features abstracted from all the forms so as to yield a single form or schema can generalize upon a series of organically related forms. Such a schema, as Brady remarks, will always be “closer to one stage of the series than it is to the others”. It cannot be equally related to them all. Yet the history of biology is replete with attempts to identify fixed schemas and to make them determinative for various biological “kinds”.

If we want to understand the relations between these leaf forms, we cannot begin with any single and definite form, whether that form be given by nature, abstracted from various exemplars, or invented by ourselves as a mediating design. Rather, "we must begin our study of the series *from the progression itself*":

> Let the reader imagine, for a moment, how one could decide whether an additional form, not included in the series as yet, could be placed within it. By what criterion could the judgment be made? (Since I have performed the experiment with luckless classrooms of students — mostly ignorant of biology — I can report that the solution is almost immediate for most observers.) The forms of a graded series have the peculiar property of appearing to be arrested stages — we might call them "snapshots" — of continuous "movement". If we begin with the first leaf (lower left) and follow the transformation to the last (lower right), we have the sense that we are in fact watching the form on the lower left turn into the form on the lower right. Because we "see" the series in the context of this imagined or "intended" movement (to use the phenomenological term), an adequate criterion for accepting or rejecting a new member is near at hand.

Understanding what is meant here by "movement" is the decisive thing. Brady helps us along with a series of succinct observations.[6]

The movement is continuous and ideal. The formative movement from leaf to leaf in an ordered series becomes more vivid to the degree that more transitional forms are supplied between the shapes we already have:

> The movement we are *thinking* would, if entirely phenomenal, be entirely continuous, leaving no gaps. Thus as gaps narrow[,] the impression of movement is strengthened, and the technique by which a new form can be judged consists in placing that form within one of the gaps or at either end of the series and observing the result. When the movement is strengthened or made smoother the new form may be left in place. But if the impression of movement is weakened or interrupted, the new form must be rejected. Thus the context of movement is itself a criterion by which we accept or reject new forms.

But note: while the movement may be said to *produce* sensible forms, the movement itself is neither sense-perceptible nor physical. Yes, each physical leaf goes through its own unique and continuous development, as does the plant as a whole. But the unifying movement, or "gesture", we recognize in passing from one leaf to the next is apprehended only in thought and imagination. One leaf does not physically metamorphose into the next leaf. So our practical and *objective* criterion for recognizing candidate leaves and correctly placing them in the sequence is an *ideal* movement.

The formative movement requires both difference and sameness. A critical point: "The impression of 'gradual modification' cannot depend any more on what each form has in common with its neighbors [such as an overall tripartite form] than upon what it *does not share* with them. Change demands difference, and continuous change, continuous difference". That is, a transformational series is united as much by differences as by similarities. We cannot have transformation without differences, and the nature of the differences tells us about the nature and distinctive unity of the transformation. One sort of transformation will require very different differences compared to another sort of transformation.

And so we are able to "see" the movement from form to form "only by a distribution of sameness and difference between them". We test in our imagination the dynamic context — the smooth movement that expresses a differential within the context of a unifying gesture — because by this movement *"the lawful relation between the forms is made manifest"*. All this normally happens without our noticing it. But if we want to understand biological form, it can be well worth noticing what we usually ignore.

An awareness of the movement changes our perception of the leaves. In seeing the movement that unites the forms, we shift our intentional focus "from text to context, from the individual particulars to the unifying movement". This necessarily changes the way we see the individual leaf, which now becomes merely an arrested stage of the movement — a momentary expression or visible trace of a passage — rather as we can isolate a series of still shots from a movie.

We can see how this works by considering an extreme case where we are given just the following two leaves of the sequence:

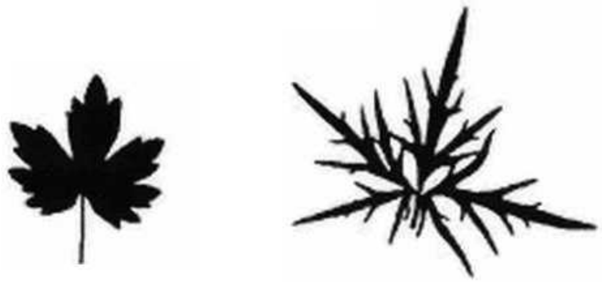

Figure 12.5. Two leaves from the buttercup leaf sequence. See text.

If we were seeing these for the first time, we could hardly regenerate an entire series of buttercup leaves from them. But if we first live with the more complete series, entering into the implied movement, and if we then look again at the two isolated leaves shown here, they will "no longer seem unlike. They will, in fact, bear a distinct resemblance to each other, and bear it so strongly when the trick is learned that the impression arises that they are somehow *the same form*. Here is the intuited 'single form' of the series, but it cannot be equated with anything static" (underscored emphasis added).

By expressing not just abstract sameness, but also a differential running throughout the series, the movement “specifies the forms possible to the series”. Here, in this movement, we have truly generalized upon the entire series in a way that no abstract and simplifying reduction to common features and no fixed image would allow. What the common schema fails to provide is “the differential that runs throughout”.

If there were no differential — if the image above showed two identical forms — then we would have no way to identify any sort of transformative movement. But because there is a differential, our enlivened and mobilized imagination can recognize in each sensible leaf the one true “leaf” capable of generating it. This is not a physical leaf, but rather the *single movement* out of which the sensible leaves have “fallen”. Thanks to our apprehension of this movement, the sensible leaf is no longer perceived as merely itself, but as a manifestation of a gesture.

The movement manifests itself through the particulars. It might seem odd to speak of movement rather than a *thing moving*. But what seems odd for contemporary habits of understanding may be exactly what’s required for overcoming the limitations of our understanding. After all, we have no difficulty speaking of the “movement of thought” — which may, in fact, be an aspect of what we are talking about here. And, in any case, it is not so difficult to see that no static form or particular thing can capture the quality of a movement *between forms*.

And let’s note also that we *are* talking about qualities here. We cannot grasp whatever is distinctive and significant about a gesture of any sort without a qualitative movement of our own thought. Only in qualities do we find the kind of multivalent potentials that can unify different (and otherwise disconnected) expressions or forms. Where a quantitative science might see in qualities only vagueness, a qualitative science gains access to dimensions of reality hidden to quantitative approaches.

The conclusion of all the foregoing (which will require further elaboration) is that “The movement specifies forms … by generating them”.

> The movement … is a continuity which must contain, in order to be continuous, multiple *Gestalts*. Thus the movement is not itself a product of the forms from which it is detected, but rather [it is] the unity of those forms, from which unity any form belonging to the series can be generated. Individual forms are in this sense “governed” by the movement of the series in which they are found — their shape and position in that series are both functions of the overall transformation.
>
> At this point in the argument, the project of description must permanently shift from static to mobile form, for the latter generalizes upon the former.

So how do we come to terms with a generative movement that is not a material thing? This will bring us to the culmination of Brady’s presentation.

The question of causality

We have been trying to understand the "movement" at work in the leaf sequence as a *form-making* principle. But, Brady remarks, if we are justified in speaking of this movement as a *making* principle rather than a *thing made*, then we seem to be attributing causal efficacy to the movement.

But we have so far been engaging in a purely descriptive project. Can such a project, however accurate, thorough, and fruitful for understanding, yield a causal principle? Brady's concern was to identify the characteristic features of the leaf sequence produced by a particular plant — the features by which we recognize "this plant is a specimen of *Ranunculus acris*". What's decisive, it has turned out, is not a particular static form or material entity, but an imaginal movement with its own distinctive qualities.

Having enabled us to recognize this movement for ourselves, has Brady also given us a causal understanding? Do we now see an *enabling power* by which the leaves manifest as they do?[7]

Current mental habits make it easy for us to picture *things* producing a well-formed movement, but very difficult to believe an ideal movement could somehow govern the production of things. This is the mentality Brady would have us overcome, and in a section of his article entitled "Form and Potency" he proceeds by refining his analysis of our experience with the buttercup leaves. Again we look at key points in his discussion.

Each individual leaf is "coming from" and "passing to". When we grasp the unity of the leaf sequence, we have recognized the differential underlying the transformation of one leaf to the next. The experience is dynamic, and this changes our perception of the individual leaves. As a result, as we discovered above, even two leaves from different parts of the sequence can strongly suggest the character of the overall transformation. The individual leaf at this point is not perceived as a mere fixed form, but rather as a movement "caught in the act".

> As our familiarity with transformation sequences increases … so does the capacity of a single form to bring other forms to mind, or of two forms to build a connecting bridge between them. The morphologist not only "sees" that two distinct configurations are still "the same", but is made aware, by the same faculty, of nascent potentials that seem to arise from every juxtaposition. This peculiar potency of organic form has acted as a constant spur to thought, and a fair amount of theory — including speculations on "vital force" and "final cause" — has responded to it.

As for vital forces and final causes, we can perhaps understand how easy it has been for observers to imagine them. What is *making* each leaf conform to the pattern revealed by its predecessors and successors, if not some special sort of force? And doesn't the directionality of the overall sequence suggest a goal that can be thought of as the final cause?

But Brady, as we will see below, finds no justification for vital forces or final causes. He wants nothing more than to clarify observation, and his fascination is with the way a perceived form relates to potential forms, given the right sort of transformative context. In this way the individual forms lose their independence. As an "arrested movement" — as a phenomenon *arising from* a predecessor and *developing toward* a successor — each leaf is inseparable from a before and after. This is how it so powerfully suggests the “missing pictures” of the transformation. “The single image now becomes transparent to the whole ‘gesture’ — which it now seems to express … Potential forms come to mind because they are contained in the whole we are trying to see”.

The point is crucial enough to bear repeating in slightly different words. Once we have established the context of movement, each individual leaf — by *coming from* something and *passing to* something — “represents, to our mind, more than itself — it can no longer be separated from its before and after. Indeed, its only distinction from these moments lies in the conditions of arrest — i.e. we see it ‘caught in the act’ of becoming something else”.

The sensible (visible) form shows itself to be but a partial disclosure of a forming activity. The instant it loses (due to our weakened perception) the *coming from* and *passing to*, it ceases to offer this disclosure. It then appears cut off from its own fuller reality — cut off from the reality and the whole in which it essentially participates, from the reality where we must look for causal relations, from the whole that is “somehow all the forms at once”. *So the recognizable truth of the individual leaf is lost when it is detached from the ideal movement, the dynamic context, out of which it arises.*

Whatever specifies the appearance of forms in time has causal significance. We come, then, to the heart of the matter.[8] Just as, in space, we can represent a set of distinct loci as a spatial unity (whether the unity of an imagined triangle or a single tree), so, too, we can represent successive manifestations in time as a unity. *“A principle by which we represent the distinct moments of time as a unity, even as we represent the loci of space as a unity, is a principle of form. But this sort of form must be a causal principle as well”* (emphasis added).

When we have a principle that tells us, consistently and correctly, something about *what we can expect to happen next* — what will follow a preceding event, so that the two events can be understood in terms of a single patterning idea — such a principle accords with what we usually think of as causal explanation.

As we have noted, the individual leaf form, insofar as it discloses a larger context of movement, contains within itself a *“felt potency to be otherwise*” — the sort of felt potency that leads some people to speak of a vital force. But the essential thing to realize, according to Brady, is that *“the sensed power is at the same time logical necessity”*. We are aware of this necessity when, presented with a buttercup leaf not currently shown in the leaf sequence, we find that it *must* be placed at only one location; otherwise, it will violate the living dynamism of the sequential movement.

The idea of logical necessity here tells us that the “sensed power” is not just brute, formless power, but a specific shaping power with its own character, or necessity. This dynamic principle remains itself only through its ability continually to become other in its successive incarnations, thereby maintaining its identity as a consistent principle of transformation. If the generative principle (or archetypal idea) were not determining a successor in this way, it would no longer be the unifying truth we have objectively recognized in the leaf sequence. We discover in it the necessity and power of change — and do so without adding any prejudicial theoretical structure to what observation yields.

> It is clear that the sense of power is part of the logical structure of the form, and not a subjective reaction on our part ... once we have accepted the dynamic context the rest follows of its own necessity rather than by any further choice on our part.[9]

In general, we recognize causation when we see one event following another in what we think of as a lawful manner — that is, according to a discernible pattern that reflects one or another sort of ideal necessity. Nevertheless, I suspect that some readers may still have difficulty believing that the kind of ideational or archetypal formative movement Brady has identified in the buttercup leaf sequence plays a role we can properly think of as *causal*. In the next section I offer further supporting commentary.

A clarification of dynamic form as cause. The idea that the dynamic, generative form we've recognized in the leaf sequence — a form or potency we've been calling a "movement" — should be viewed as causal immediately raises a question for most people: "But what is *making things happen?*" Where is the necessary material influence, the matter impinging on matter, the coercive gears and levers that bring something about? How can an immaterial form, however dynamically we imagine it, causally intervene in the growth of a plant?

The questions are understandable in the light of contemporary thinking. But this does not absolve them of extreme naïveté — a naïveté that Aristotle had already overcome when he recognized what he called "formal causes" at work in material interactions.

The fact is that *all* material causation is an expression of immaterial (ideal) relations. Bodies moving at random in the solar system would tell us nothing about causes or laws; but if we observe certain geometric regularities — movements, for example, tracing the forms of conic sections such as ellipses or parabolas — or if, in investigating the fall of objects toward the earth, we eventually arrive at the formulas, $F = ma$ and $F = Gm_1m_2/d^2$, then we have discovered a certain lawfulness. We can talk about material objects acting on material objects, but without conceptual relations such as these — and conceptual relations are *not* material things — we have no lawful regularity and therefore no causation at all in any defensible sense.

Biologists today remain determinedly focused on material manifestations rather than on the living activity through which the material organism takes shape. Their conviction is that what has already become determines what *will* be. Brady's discussion of leaf sequences shows how wrong this is. The already manifested leaves, as material achievements, do not cause or explain the form of the next leaf. Rather, they, along with all the forthcoming leaves, testify to the ideal movement that has given rise to them and rules them.

We can say much the same thing about the developmental processes we observe in complex, multicellular animals. Nowhere along the path from the zygote to the mature form is the future form determined by what has already come to manifestation. That's why (to take a more extreme example), if we were seeing an insect larva or a tadpole for the first time, we would have no ground for sketching a clear picture of the butterfly or frog to come.

And, as we saw in the discussion of RNA splicing and Paul Weiss' work in Chapter 6, even at the molecular level the freedom of movement ("degrees of freedom") possessed by molecules in a fluid medium makes it impossible to treat the outcome of elaborate molecular operations as if each step were strictly determined by the material result of the previous step.

So the rule in biology is this: while the previous material achievements may be required (as preconditions) for whatever comes next, they do not *bring forth* the next steps. The failure of a materialist biology to reckon with this truth has distorted the entire science. And the failure extends all the way to evolution. As my colleague, Craig Holdrege, has summarized it, “You can’t grasp evolution by staying with its material products”.[10]

Threefoldness, the biology of form, and evolution

In 1977 the German biologist, Wolfgang Schad, published a substantial volume called *Man and Mammal: Toward a Biology of Form*. The richly illustrated book was founded so fully upon direct observations, and these observations required so thorough a reconceptualization of the foundations of biology and evolution, that biologists could scarcely afford to take note of it. So (for the most part) they didn’t.

But Schad never ceased his undertakings, and in 2020 there appeared in English translation a vast, 1300-page, two-volume, hardcover expansion of the original work, with hundreds of color plates and with a new title: *Threefoldness in Humans and Mammals: Toward a Biology of Form*. It’s all there, ready to be taken in by any with the requisite interest and willingness to see the biological world with new eyes. Here I can offer only an inadequate sort of abstract merely gesturing toward the broader themes of this work. It will be enough, I think, to suggest how little the problem of biological form in relation to evolution has yet been recognized by the biological community as a whole.

Schad acknowledges how much biologists have learned about “genetic factors, basic physiological processes, predictable instinctive reactions, and the social behavior of animals”. But we can in this way learn a great deal about the physical parts and developmental processes of an animal without coming to a recognition of the formative ideas governing these processes. Similarly, explaining any organism in terms of genotypes subject to natural selection under the pressure of environmental conditions still leaves us wondering *what the organism has to say about itself through its own unique form*.

About the beaver, Holdrege remarks that its “teeth are good for gnawing wood, the large flat tail for swimming and as a paddle to slap against the water to alert other beavers about the presence of potential predators, and the high-set eye sockets for swimming inconspicuously with its head only slightly above the water surface”. All this sounds good in terms of fitness and survival strategies. And yet what does it tell us about why the beaver took on its own specific, unified character and fashioned its own special niche within a larger environment inhabited by so many other organisms that traversed very different adaptive pathways? The conventional approach

> leads us to mentally dissect the animal into different traits, each of which has its own type of survival value. The coherence and integrity of an animal dissolves into a collection of traits, and all its characteristics are considered solely as adaptations that secure survival (Holdrege 2019).

But we have already seen that, if we looked at the leaf sequence discussed above without attending to its unifying idea, we would miss a decisive causal truth about its character. Similarly, by limiting our attention to the survival value or "fitness" of different animal traits — traits that *could* have taken countless other forms — we remain ignorant of the expressive unity of the specific animal. "No one", Schad says, "can tell us why well-known hoofed mammals, like cattle, deer, and rhinoceroses, have head protuberances, while horses, donkeys, tapirs, and camels do not. Neither molecular biology nor behavioral research concerns itself with the significance of an animal's form" (Schad 2020, p. 2).

David Seamon, editor of the journal, *Environmental and Architectural Phenomenology*, and co-editor of the book, *Goethe's Way of Science*, wrote of Schad's work:

> In the holistic biology that Schad presents, each feature of an animal is seen as significant because the whole is reflected in each part. The aim is to recognize the inner organic order in an animal in such a way that its individual features can be explained by the basic organization of the animal itself (Seamon 2020).

A starting point: living polarity in the human being

Schad attempts to appreciate organisms in the living terms that have long been recognized by the best biologists as essential to any profound understanding. I mean the terms of a dynamic interweaving of activities whereby parts come into being and gain their specific identity, not as independent elements, but rather as integrated expressions of a pre-existing whole.

The key to Schad's approach lies in his understanding of the organism as a being organized according to principles of polarity. By "polarity" he does not at all suggest what is usually meant by "polar opposites". There is no absolute opposition or incompatibility of parts. Rather, we see a mutual participation of parts within an integral whole that lives by reconciling the creative tension between opposing tendencies.

A merely static image of polarity is given by a bar magnet, each of whose poles extends as an active principle all the way into the opposite pole. Cut a small slice off one end of a bar magnet, and you have a second, smaller bar magnet with the same "opposition" of two poles. Each pole's character extends all the way to the opposite pole, and can exist only in conjunction with the activity of that opposite pole.

Our own human organization is a good place to start in seeking a more living example of this "unity of contrary tendencies". But here we discover, as with organisms generally, that this unity is not merely bipolar in the manner of an inert bar magnet. Rather, the active, living interpenetration of the two poles points to a third aspect of our being — a rhythmic and harmonizing activity that mediates between the poles, effectively raising the contrary tendencies to a higher level where unity is achieved.[11]

And so, looking at the human being, Schad sees three functioning systems. One is centered in the head, one in the abdominal cavity and limbs, and one — mediating between the other two — in the chest region.

In the head we find gathered together most of our sense organs, through which we more or less consciously relate ourselves to the “outer” world — for example, through sight (eyes) and our sense of balance (inner ear). The center of our nervous system (brain) is enclosed in a protective, globe-like exoskeleton, comprised of bones largely fused together.

At the other pole we find our limbs, with their endoskeleton. Far from globe-like and fused together, the parts are linear. The bones are connected by elaborate joints allowing the relatively independent movement of parts. The puzzle here might be that Schad conflates the limbs with the abdominal cavity and its intense metabolic processes, as if they comprised a single, coherent system.

What the conflated functional aspects have in common is a power of movement, where “movement” is used in an older (Aristotelian) sense, overlapping with the sense of “change” (*metabolē*). Motion, according to Aristotle, can be of several types, involving change in identity, quality, quantity, or place. “The last named is the primary kind of motion but involves the least change, so that the list is in ascending order of motions but descending order of changes” (Sachs 1998, p. 249). Of course, our movement in space makes intense demands upon our metabolism for energy. We can also say that both the metabolism and the limbs serve to maintain an animal’s autonomy from its environment. They do this physiologically — through the digestion and assimilation of “alien” food into the structure of one’s own body — and in terms of the ability to relocate oneself in space (p. 16).

The organs of digestion in the abdomen are not invested with, or protected by, a bony structure, but are an altogether soft part of the body. Their activity, contrasted with the almost “inert” quality of the brain and its nerves — and also contrasted with the functioning of the limbs — consists of intense *internal* movement. This includes the muscular and mechanical movement of the digestive organs, but also, and most prominently, the transformation — breaking down and building up — of substances.

In this way Schad refers to the *nerve-sense system* on the one hand, and the *metabolic-limb system* on the other. In between, in the chest area, is the *respiratory-circulatory system*, or the *rhythmic system*, centered in the activity of lungs and heart.

This middle region of the body is marked by a transition from the character of the head region to that of the abdomen and limbs. It is surrounded by the partly open rib cage, where the relatively immobile bony structure toward the head is more closed-in, with the ribs circling all the way around from the backbone to the sternum. But lower down the ribs become gradually shorter, straighter, and more mobile, “the last two pairs remaining close to the spinal column, where they ‘float’ freely and point downward. The sternum is broadest near the head and relatively narrow where it ends only part way down the chest cavity” (p. 18).

Here in the middle region we do not see a battle between the two poles, but rather a harmonization of them. The rhythms of breathing and heartbeat bring the breath and oxygenated blood to every part of the body, maintaining complex processes of balance or homeostasis.

> Lungs and heart are rhythmically pulsating organs. In each, contraction and expansion, tension and relaxation, compression and dissolution alternate constantly. The polarities of the organism, therefore, are always present in this region, but here they do not maintain their spatial separateness; rather, they actively complement one another through their rhythmical alternation in *time* (p. 16).

That is, this middle system is itself a manifestation of polarity, but through rhythmic alternation the poles are fully reconciled with each other. We see this polarity expressed in the relation between lungs and heart, where

> the lungs tend more toward the upper processes of the body that are centered in the head. Through the trachea, the lungs reach up into the head and establish a direct connection with the outside world … Their passivity, much like that of the head, appears also in the fact that they are incapable of self-initiated motion and are moved by the thorax and diaphragm. (pp. 16-17).

The heart, on the other hand, “initiates its own movement” and is “closed off from the outside world”:

> The largest of the arteries originating in the heart, the aorta, turns downward toward the lower part of the body, where the blood relates directly with the processes of the metabolism. Only through the circulation of the blood do the lungs have access to the dominant processes of the metabolism; conversely, the blood gains contact with the outer atmosphere only through the lungs (p. 17).

Interpenetration of the three aspects

Referring to the relative immobility of the head, Schad writes: “Above the runner’s flailing limbs and panting chest, the head quietly keeps the goal in view” (Schad 2020, p. 15). But here we need to keep in mind that the threefold aspects of the human being are neither abstract principles nor the material end-products of activity. What we find are qualities of character that continually interact and mutually influence each other, much as motifs, themes, and harmonies may play into each other throughout a musical composition.

It is clear enough that the nerves are not only contained in the brain, but also extend throughout the body, just as do our senses, which give us awareness of many internal processes of our body. Likewise, our circulation and breathing do not exist only in the heart and lungs. The circulating blood, with its finely balanced gases, flows throughout the body, and the breathing function includes the nose, mouth, and vocal organs. And so, too, metabolic activities proceed not only in the digestive organs, but in every cell of the body.

There are other ways we can look at this functional interplay. An example is given by the way our own head organization not only represents one of the poles of our being, but also bears within itself a somewhat muted image of our whole, threefold being. That is, the head has its own opposed (upper and lower) poles as well as a reconciling middle. The nervous system comes to a clear focus in the immobile, bone-enclosed brain. At the opposite pole we have the “limb” system manifesting in the movable, hinged, lower jaw. With its chewing motions to grind food and the digestive processes initiated by saliva, the jaw brings metabolic-limb activity to our heads, where this activity “establishes direct contact with the outside world (p. 19). And through our breathing and speech we see the performance of the middle (rhythmical) system. One way Schad makes this latter point is by referring to the air-filled cavities “found in the middle section of the cranium, between the sensory area of the face and the braincase itself”:

> They include the larynx, the cavities of the throat and nose, and the more ossified air-filled cavities in the upper jaw (maxillary sinuses), middle ear, and frontal and sphenoid bones. Here, in a delicate way, the head’s own respiration takes place. When the lungs exhale, air is pressed into the head’s cavities; when the lungs inhale, the cavities of the head exhale. These cavities are lined with a moist inner layer that allows for gaseous exchange. Thus the middle region of the head also participates in respiration and in the organism’s rhythmic functions (p. 19).

Furthermore, even when we look only at the mouth and throat we find all three aspects of the organism coming into play. The forward part of the mouth, with the sensitive lips and tip of the tongue, manifests the dominance of the conscious nerve-sense pole, whereas the middle system comes to the fore in the rhythmic chewing activity. Finally, the food is (with a diminished role for consciousness) moved to the rear of the mouth, swallowed, and passed down into the unconscious, metabolic center of the body (p. 40).

Despite all this mutual interpenetration of functional characteristics, we can certainly say that the nerve-sense system is *centered* in the head, just as the rhythmic system is centered in the chest and the metabolic processes in the abdomen.

A great part of Schad’s research consists of a kind of “musical” analysis whereby he traces the endless lawful interplay within the threefold organization of the body. We will see more hints of this subtlety before we finish our discussion of his work.[12]

Threefold organization in mammals

It is commonplace to note that many animals possess specializations that make them, in one regard or another, superior to humans. The sight of an eagle, the dog’s power to follow a scent, the gnawing ability of a beaver, the digging skill of a gopher — we could scarcely hope to match these abilities with our own natural equipment.

Humans, we might say, specialize in non-specialization. Our hands and arms, good for neither digging nor flying, neither swimming nor swinging from tree branches, can employ an endless range of tools of our own devising, from computer keyboards to the knitting needles through which we have long fashioned clothing adapted to numerous environmental conditions. While we lack the well-developed instincts that fit animals for particular environments, our brains remain plastic throughout our lives in decisive regards. “Most of the regions of our neocortex have to be differentiated through active learning. We can change established habits and continue learning indefinitely without ever exhausting the functional potential especially of the right hemisphere” (p. 10).

A central truth found in Schad’s work is that the various mammalian groups develop the threefold organization of their lives with different balances among the three functional systems.

In other words, they can “specialize” not only in specific behavioral traits or morphological features, but also in one or another of the three functional systems.

For simplicity, Schad’s work is often presented initially by focusing on three groups of mammals. One group shows an especially strong development of the nerve-sense system, one emphasizes the polar opposite metabolic-limb system, and one reflects especially well the principles of rhythm, harmony, and balance characteristic of the middle system. These are, respectively, the rodents, the ungulates (hoofed mammals), and the carnivores.

Mice, with their nervous sensitivity and refined sense organs, exemplify the emphatic nerve-sense development typical of rodents. This is evident even in the limbs of rodents, which tend to be small and delicate, with long and narrow fingers and toes, and nails shaped like tiny claws. “The forepaws of squirrels, for example, are adept at grasping, handling, and feeling. Their limbs have acquired a sensory function. Long sensory facial hairs (whiskers), and shorter ones over the entire surface of their body including their bushy tail, project beyond their warm coat and enable squirrels, fitfully twitching and hopping, to find their way in the surrounding world … Agile and quick in its reactions, a rodent lives in constant agitation, alarmed pauses, and rapid flight. Even in sleep, nervous spasms periodically run over its small body” (p. 38).

This differs greatly, for example, from the powerful digestive processes and strong, hoofed limbs of the ungulates such as the dairy cow. “In contrast with the five-digit type of limbs of the less specialized mammals, the ungulates’ feet have regressed to a few bones, which, however, are very strongly formed. This specialization of the limbs extends even to the powerful enlargement of the nail into a hoof … The limbs of horses and cattle support massive bodies and, in stamping and galloping, horses express the powerful, animating forces within them” (p. 38).

Whereas a mouse must eat frequently, preferring energy-rich, easily digested foods and leaving behind dessicated droppings with little fertilizer value, the ruminants (which Schad considers the “most characteristic” group of ungulates) are well-known for their four-chambered stomachs, their extremely long intestines, and their ability to digest cellulose.

> Contented peace and restfulness suffuse the cow’s placid gaze, especially when, ruminating for hours, she devotes herself entirely to her food. Her eyes, and the eyes of all ruminants, lack the yellow spot, the *macula lutea*, which is the part of the retina with clearest sight. To the ruminants, the outside world appears diffuse. They have a stronger experience of smell and taste, senses more connected with the inner working of the metabolism than the eyes and ears. A cow is never as completely awake as a mouse; the unconscious processes of digestion predominate even in the ruminant’s state of half-wakefulness. (pp. 38-39).

The carnivores, with their intermediate character, which lacks the distinctive and one-sided development of the rodents and ungulates, are less easy to describe. Schad spends a good deal of time working out the sometimes subtle ways in which different groups of carnivores lean slightly more toward the nerve-sense pole or the metabolic-limb pole, while generally falling in the broad middle area between the two poles. (See his discussion of dogs and cats below.)

It happens that organisms in each of the three major groups tend to fall in different size categories. Rodents are smaller, ungulates larger, and carnivores take up a position between them. And there is an inverse relation between size and the quality of the food each group favors. Rodents prefer highly nutritive, energy-rich foods — fats, oils, and starches. Breaking these down for immediate use, they tend to store very little in the way of bodily reserves of energy. Ungulates, on the other hand, eat poor-quality food, and build up from it great energy reserves — illustrated by the hump of a camel or the subcutaneous tissue (ham) in pigs. And so,

> While nervous constitutions characteristically break down substances, metabolic ones rebuild and augment them. The nutritive processes of the carnivore represent an intermediate state. When a leopard devours a gazelle, a true change of substances does of course take place during digestion, but the change from one form of protein to another hardly alters the chemical energy level (p. 40).

Schad notes what might almost seem a counter-intuitive relation between, on one hand, the nerve-sense or metabolic-limb emphasis and, on the other hand, the overall form of the animal. The rodent, with its strong nerve-sense orientation, tends toward an accentuation of the posterior end of its body, with long tail and the hind legs longer and stronger than the forelegs. The head is not dramatically separated from the rest of the body (think of the mouse). For a rather extreme example of this posterior emphasis, see Figure 12.6.

By contrast, the American bison, with its highly developed metabolic-limb system, presents an anterior emphasis, with its powerful neck and head, and the great hump above its shoulders (Figure 12.7). The giraffe, with its long neck and forelegs and its even more “shrunken” hindquarters is an extreme example of this tendency.

Figure 12.6. Taxidermied lesser Egyptian jerboa at the Natural History Museum in London.[13]

Figure 12.7. An American bison.[14]

The carnivores in general occupy the middle ground, where balance is achieved between the posterior and anterior ends of the animal (Figure 12.8). Or one can picture the chase, where a lion pursues its prey with a burst of energy, its forelimbs and hindlimbs contributing equally to the task. And then, in the natural rhythm of its life between sudden exertion and inactivity, the great predator, having eaten its fill, is overtaken by lassitude. Its rest and sleep are the very picture of flexible bodily relaxation.

Figure 12.8. Female tiger.[15]

Compare that with the ungulates:

> [Speaking at first of the bison:] The front pole of the body with its morphological over-accentuation constitutes the animal's center of gravity. When cattle stand up, they first straighten their less heavily burdened hind legs; only then do they raise the heavier, front part of their body. They lie down, too, in a way that seems strange to us: First, they bend their front legs, laying the main burden of their body down upon the ground, and then the hindquarters follow effortlessly …
>
> In a rodent — a squirrel, for example — the posterior limbs and the tail are over-accentuated. The lighter front part of its body and its smaller forelegs are less ponderous than most ruminants', enabling it to sit up on its haunches and raise its head, which is quite typical for all mice, hamsters, dormice, chipmunks, ground squirrels, marmots, beavers, etc. This is quite the opposite of the buffalo, whose mighty head is bowed down by heaviness (pp. 294-5).

Subtle interweaving

I mentioned above that a certain threefoldness manifests within the "one pole" of the human head — and again within just one part of the head, the mouth-throat area. (Schad also discusses at length how the teeth alone strongly manifest a threefold nature.) This illustrates the general principle of "the whole within the part".

This kind of interweaving is in fact evident everywhere. But it occurs in a continually different expressive fashion. Schad subtly traces the differing relative prominence of the three functional systems not only in the three major groups (rodents, carnivores, and ungulates), but also within many of the subgroups as well as entirely different major groups. He shows, for example, how, in two subgroups of carnivores — felines and canines — we see a degree of leaning toward either the nerve-sense or the metabolic-limb pole. This is despite the fact that both groups clearly exhibit, overall, the rhythmic or middle emphasis of the carnivores.

Cats, with their highly developed senses of sight and hearing, and their sensitive whiskers, tend toward the nerve-sense pole. The dog's primary orientation is toward that of the rather duller sense of smell. "The cat's sensitive constitution is also revealed in its paws, with their retractile claws, so different from the dog, whose limbs have become tools for running, with immovable claws" (p. 48).

As for the cat, "even its method of hunting is in keeping with its strongly developed senses: it prowls stealthily, then crouches motionless with all its senses focused on its prey, and finally pounces with lightning speed. By contrast, wolves, as well as their descendants, the dogs, hunt by pursuit. Tirelessly, they drive their victim until it is exhausted and must surrender. Cats hunt primarily with their senses, thus avoiding great physical exertion; dogs hunt with their limbs, powerfully activating their metabolism. Dogs and cats have thus developed polar modes within the 'attack' behavior of all carnivores … And yet in their supple agility, well-proportioned form, and moderate size, both are typical carnivores, shaped primarily by the rhythmic system" (p. 48).

Briefly: we see a similar polarization within the ungulate group. With its strongly developed digestive system, the bison (or cow) exemplifies the least development of the nerve-sense pole, while the giraffe, with its more refined head raised high above its digestive organs and alert to the larger environment, shows a relatively strong nerve-sense emphasis. And just as the lion and wolf occupy a middle place among the mammals generally, the deer, with its nerve-sense and digestive functions more or less in balance, holds a middle ground among the ungulates.

I hope all this illustrates a crucial truth. We are not talking about fixed schemas and opposing structures, but rather about qualitative tendencies that can play into each other with infinite subtlety and variation. Clearly, as with all qualitative science — and as illustrated by our discussions of the sloth and plant leaf sequences above — science must engage with art in the effort to apprehend the morphological and functional characteristics of animals. The faithful grasp of polarity requires a lively imagination immersed in the rich world of phenomena.

To a bench scientist in the laboratory, bent on uncovering unambiguous causes and “master molecular regulators”, it may seem that a qualitative science is no science at all. And yet, to anyone profoundly attuned to the living world, it is within the laboratory that, all too often, the organism disappears and biology comes to a dead end.

Can evolutionists escape responsibility for explaining these patterns?

It’s worth mentioning that the polarity we are speaking about here bears strongly on evolution. The differing but ordered qualitative emphases among the different groups of mammals are invisible to current evolutionary theory. So we are forced to ask, “What is missing from this theory?”

The observed patterns, according to Schad, include this one: Within any group there is an evolution from smaller, more active, nerve-sense-dominated animal forms toward larger, less active, metabolically oriented forms. The latter represent a kind of conclusion, after which evolution takes up a fresh start from another point, just as, upon the extinction of the dinosaurs, the tiny mammalian forms existent at the time became the basis for a new evolutionary thrust.

Such regularities of form can hardly be understood in terms of conventional evolutionary theory. Someone else who appreciated the difficulty of the problem of form relative to contemporary concepts of evolution was the widely respected twentieth-century Swiss zoologist, Adolf Portmann, as evidenced by his observations in a book that has been translated into English as *Animal Forms and Patterns — A Study of the Appearance of Animals*.

By paying attention to form, Portmann recognized trends and relationships overlooked in standard approaches to evolution. He found the external appearance of animals to be the self-presentation of creatures with an inner way of being — a presentation that includes ways of perceiving, moving, behaving, and all forms of color and shape expression in space and time. This expressiveness with its meaningful patterns, he claimed, goes far beyond what might be advantageous relative to natural selection.

Portmann offered a simple, but useful reminder of the expressive luxuriance of nature when he mentioned in passing how plants present us with “a variety of leaf shapes in a profusion of unsuspected magnitude” despite their not being “favoured by any animal selection”. That is, the leaf shapes cannot be explained by selective pressures such as those that might involve the leaves and the insects that feed on them. Similarly with “the many varied types of design on the shells of snails and bivalves”, and also with “the whole world of astonishing shapes found in the shells of the microscopically small, one-celled Radiolarians of the open sea” (Portmann 1967, pp. 114-5, 124).

Portmann’s excellence as a zoologist is undisputed. But he had the misfortune of pursuing the main body of his work on the eve of the all-out triumph of molecular and genetic approaches to the organism. Few wanted to look at the animal in the qualitative manner he did, so they did not see what he saw.

Among those who do look at animal form in its own terms — and who have extended Schad’s work by applying it to their own research — we should at least note in passing biologist Mark Riegner and his investigation of the plumage patterns and coloration in birds.[16] Then there is the Welsh dinosaur expert, Martin Lockley. As a paleontologist and professor of geology for thirty-two years at the University of Colorado Denver, Lockley wrote his popular 1991 book, *Tracking Dinosaurs: A New Look at an Ancient World*, as well as numerous technical publications.

In his 2007 paper, “The Morphodynamics of Dinosaurs, Other Archosaurs, and Their Trackways: Holistic Insights into Relationships between Feet, Limbs, and the Whole Body”, Lockley wrote that within the two main dinosaur groups,

> one can detect a spectrum of form between small, long-tailed, narrow-bodied, bipedal species (posterior emphasis) and large, wide-bodied, shorter-tailed, quadrupedal species with various cranial processes (crests and horns), indicating an anterior emphasis. These same or similar formative movements reiterate at many different taxonomic levels, and even reiterate within organs of the whole organism such as skulls and feet. (Lockley 2007).

Noting that these morphodynamics of dinosaurs can also be recognized among birds and ungulates, Lockley recommended that paleontologists pay much more attention to such patterns of form, and he suggested that the "traditional emphasis on Darwinian functionalism will assume less importance, while the significance of inherent morphodynamics becomes more fully appreciated". After all, we can’t be so easily satisfied with the explanation that some particular dinosaur developed a large head “for use in combat” when we find that the movement toward larger heads happens repeatedly and lawfully — in harmonious relation to many other morphological trends — within every group of dinosaurs.

This, of course, amounts to a startling rejection of conventional evolutionary reasoning. The typical causal, deterministic language of biology is simply ill-suited to an understanding of changing patterns of form. Lockley formulates this rule: “*rather than single organs changing for specific adaptive purposes, all organs may change simultaneously as part of a shift in a complex, highly dynamic organic system*”. And what is true of the individual organism seems to be true also of the way species are ordered within higher taxonomic groups, so that “*the* *evolution of species may be, at least in part, an inherent biological dynamic associated with large-scale evolutionary shifts affecting multiple species*" (emphases in original).

This dramatic claim leads to another one of those bombshells Lockley rather casually drops throughout his paper as he unfolds the implications of wide-ranging, repeated patterns of form in the animal kingdom. He notes that different animal groups show three sequential cycles, first of posterior, then of balanced, and then of anterior development, and that the great dinosaur extinction terminating the Mesozoic era came at "*precisely* the end" of the third cycle, "when horned dinosaurs (like *Triceratops*) had developed maximum head size ... This seems to be a rather remarkable coincidence, in which a large-scale, inherent biological cycle coincides so precisely with a purported extrinsic cause (meteorite or comet impact)". He goes on:

> If a significant number of morphodynamic cycles, culminating in anterior (metabolic) specialization, also result in, or coincide with, extinction, the implication is that extinction, at least to some degree, is an inherent, biological dynamic analogous to a large-scale "life cycle".... Therefore, efforts to seek external causes may be unnecessary and result in misleading, or at best incomplete, explanations and correlations.

And in yet another jettisoning of standard evolutionary thought, Lockley questions whether evolution proceeds "by some process of random mutation." After all, given repeated and dynamic morphological tendencies exhibited widely among different animal groups and manifesting their own relational lawfulness, it is hard to reconcile these with the supposedly random generation of variation. If, as Lockley suggests, "it may be possible to predict the general form and physiology of the whole animal from an analysis or understanding of the parts", and if a similar coherence of form exists within the "superorganisms" comprising the various taxonomic groups, then we are a long way from both the usual adaptationist explanations of the features of animals, and also from chance as the primary generator of variation for natural selection to act upon.

More generally, Lockley argues for a holistic approach to animal morphology, rather than an attempt at feature-by-feature explanation. The latter focuses upon adaptive function (horns are used for butting) whereas the former reckons with the fact that in any organism the modification of one part "will lead to a compensation or ripple effect throughout the whole" organism.

Lockley's work on dinosaurs is vastly more complex and subtle than I could possibly indicate here (or properly understand in my own right). But, following Schad, he is clearly suggesting the need for radical new perspectives on evolution. Yes, we must investigate how the various features of an organism help to make it fit for the requirements of its life within a particular environment. That's part of getting to know what sort of organism (and environment) we're dealing with. But when this investigation is narrowed down to a search for survival mechanisms offering a competitive advantage — when the explanatory significance of every feature is reduced finally to the terms of a quantitative judgment about fitness to survive, so that the feature itself is not taken to express anything significant apart from its contribution to survival — when the artful pattern on the butterfly's wing becomes no more than, say, a deceit aimed at birds to avoid being eaten — then we lose the organism as such.

We lose it because we're not really *seeing* it; we're not allowing its features to speak for themselves, in their own expressive terms. Everything has to be reduced to fit an interpretation that says a feature is *for* some particular survival benefit rather than for the entire, uniquely formed way of being of the organism itself. We thereby ignore the lawful patterns visible in the way an evolving species picks one path rather than another through the infinite landscape of survival possibilities

Naturalists may develop a profound sense for the inherent lawfulness of a particular organism's way of being. But, unfortunately, naturalists do not have much standing in the age of molecular biology. As Schad puts it on the opening page of his two-volume work: "The immediate observation of nature and the study of natural science as commonly practiced today have generally become different activities". A profound truth whose disturbing implications are not often considered.[17]

If, however, it is true that the organism is a recognizable unity; if there are consistent harmonies sounding through its various "survival mechanisms", bringing them together in one song — a song as distinct from those of other organisms as a lullaby is from a patriotic march; if the organism, not only as a product but also as a shaper of its environment, takes up its creative opportunities and employs them with all the coherence and expressive focus we find in the work of a perceptive artist; if, in sum, there shines consistently through all the morphological, physiological, and behavioral details of an organism a character declaring something more than "I have survived", but also "I am my own sort of being, unified, bound by a lawfulness not only of matter but also of form, and this lawfulness is accessible to those who approach me respectfully" — well, then, the supposedly solid foundations underlying contemporary evolutionary theory will have crumbled beneath us.

Where are we now?

We Have Seen What a Qualitative Biology Can be

Despite the several-century effort within science to formulate a quantitative discipline without any explicit acknowledgment of the role of qualities, the goal is impossible to achieve, and we always in fact have an “invasion” of qualities in our science. But because the qualities go unacknowledged and are rarely if ever consciously taken up as an issue for scientists to come to terms with, the invasion generally takes unhealthy form — something I have hinted at in Chapter 13.

In this chapter I have drawn on the work of three researchers in order to present diverse examples of biological work where qualities are not only front and center, but also where the qualitative nature of the work is fully recognized as decisively important for scientific understanding. With these examples we have addressed the following questions: (1) How can we characterize the way of being of a specific kind of organism (the sloth)? (2) What sort of immaterial and qualitative understanding gives us our basis for recognizing the material, species-specific, leaf sequence patterns in certain plants? (3) Do we discover distinct and lawful relations between the forms of the various mammalian groups, and do these relations present problems for current evolutionary theory?

What then are qualities? It will be evident from the discussion in this chapter that there is no great mystery here. A qualitative language describes what a thing is in its own, observable and sense-perceptible terms — the terms that are a prerequisite for our having a conviction that anything material is actually *there*, anything from which we can, if we wish, proceed to abstract mathematical relations.

In Chapter 24 I address the broadest and most fundamental question of all: whether, within science or outside it, we can speak coherently of a material world without first taking qualities seriously.

Notes

1. (Brady 2006). The last sentence of this quote (“It is always nice to see where one stands”) is not present in the current cited source, which reads instead: “I left his office feeling very deflated. Again a representative of science had put his finger on my immaturity”. I believe the quote I have reproduced in the main text was from an earlier version of Brady’s book chapter. (I personally had a hand in the preparation for publication of the book in which Brady’s chapter appears. The book went through a number of versions under the guidance of the authors.)

2. Figure 12.1 credit: Craig Holdrege.

3. Figure 12.2 credit: Craig Holdrege.

4. Goethe 1995, pp. 57, 307. On the relevance of Goethe's scientific work to today's science, see Craig Holdrege's "Goethe and the Evolution of Science" (Holdrege 2014), an expansion of a talk given in October 2013 to an interest group at the New York Academy of Sciences.

5. Figure 12.3 credit: Craig Holdrege.

6. Keep in mind that, without our active participation in the leaf progression — without experiencing qualitatively through our own willed inner movement the character of the transition from leaf to leaf — we will not come to any full appreciation of Brady's discussion. It is, in any case, not an unhealthy exercise to bring about through our own effort the transformation of one leaf form to the next, an exercise requiring a muscular and fluid imaginal activity that habits of abstraction easily bypass.

7. It is important to realize that the movement Brady speaks of cannot by itself wholly determine leaf forms:

> The movement of the series cannot, of course, demand that any particular potential will be realized, but it does give the range of potential forms — those which would become actual were the imagined continuous transformation to become actual. Whether an actual leaf will realize this or that potential is determined by something else, but it is the movement which defines the potential forms.

Only a few out of a continuous series of possibilities are actually realized on a single plant, and the form of those few will be influenced by environmental factors. Unusually cold or dark or dry weather will have its effect — but always consistent with the recognizable potentials of the species we are looking at.

8. Brady considers form and cause in the context of Immanuel Kant's treatment of organic form in the *Critique of Judgment*. My present purposes forbid extending the discussion in this direction. But see the following footnote.

9. For the philosophically minded, Brady offers the following aside:

> I am aware of course that the coincidence of logical necessity and causality is something that one does not think to see after the work of Hume and Kant. With regard to Kant I can only point to the potential breakdown of his system that threatens to emerge from the *Critique of Judgment*. Goethe may be understood as exploiting the seeming contradiction that we can intend what we cannot understand. Of all our experiences, intentionality is potentially the most clear, for what we do ourselves is open to our intimate gaze. Kant did not attempt to observe his own intentional acts, and thus never investigated this possibility. Goethe, coming to Kant when he was already engaged in this project, was simply made more conscious of it. He read Kant as if Kant were proposing a similar "adventure of reason".
>
> With regard to Hume we must return to the problem of causality in general. It should be clear to us that however we normally think of causal necessity, we must intend it as a necessity that stretches over different moments in time, and it is the ultimate exclusion of one moment from the next that defeats Hume's attempt to think it out in terms of logical necessity. An identity that bridges that exclusion would also solve the logical problem, and just such an identity is intuited in the observations described. It should be of some interest to rethink Hume's problem on these grounds, for it rests upon the assumption that the

> distinctions of time are primary. If, on the other hand, the time-form is primary, we should discover that we must intend this unity in order to perceive the "movement of time" itself. The project is too fundamental to consider any further in this discussion.

Regarding Kant, Brady provides a succinct summary of the issues in another luminous article (Brady 1998) not currently available online:

> Kant made science into a study of appearances aimed at bringing them under rational law, that is, if we could understand and predict appearances, our inability to understand their ultimate source would not be a serious debility.
>
> Unfortunately there were some appearances that resisted this project. Kant was acutely aware that our notion of life was formed by the sense of inward unity, an agency that produced and governed the organism from within. This inner agency could not be brought to the understanding by a conceptual summary of its parts, as is the case with inorganic compositions. In its earliest stages, in fact, the organism had yet to develop the organs by which its later existence would be supported, making the inward unity *antecedent* to the developing parts, a whole which makes its own parts necessary rather than a result of the combination of the parts. To the degree that the combination of parts may be said to be causal, each part aided in the production and maintenance of all the others, and all the others did the same for each. As a result, the physical organs had to be recognized as both cause and effect of themselves. The linear chain of causes by which mechanical events were understood here curled up into a circle, depriving the chain of explanatory power.
>
> If one reflects more deeply, it seems obvious that the mechanical laws do not show the requisite logical structure to explain life. Inert objects were moved from without by impressed forces. Laws governing their movement, therefore, are also "external" to the things moving, that is, the laws of mechanics sum up the interactions of objects while being perfectly indifferent to the individual natures of those objects. The organism, however, could not be known in this abstract manner, and predictions concerning its changes were dependent on a knowledge of the species. Even the sort of materials out of which it was constructed are an expression of species identity, and thus the governing laws had to be identified with the object they governed, that is, such laws not only governed, but also produced, their objects. Or, at least, Kant argued, these results express the way things *appear* to immediate perception …
>
> Analytic thought, which understands the whole through summing the effects of the parts, could not comprehend a whole that preceded the parts or accomplish a path of thought that moved from the general to the particular. Such a movement, Kant argues, would be that of an *intuitive* intellect, which humanity does not possess.

Brady goes on to say that, while Kant never made a project of actually testing whether a properly developed scientific understanding could embrace the becoming of an antecedent, organic whole, this was exactly the test that Goethe did make — and made successfully, as shown by his work on plants.

10. Craig Holdrege, personal communication.

11. Schad's "threefold" understanding of the human being draws from the threefold picture first offered by Austrian philosopher Rudolf Steiner in his 1917 book, *Von Seelenrätseln*. That work has been translated into English under various titles, including "The Riddles of the Soul".

12. Schad's description of the relationship between the organism and the world shows the impossibility of any rigidly schematic notion of threefoldness:

> Initially, I characterized the whole upper system as *directed outward toward the world*, and the lower system, by contrast, as *self-enclosed*, with the rhythmic system mediating between the two. Though this relationship is an essential characteristic of the threefoldness of the bodily organism, we can, as we have also seen, come to a more nuanced understanding of this pattern in its particular characteristics. On the one hand, the organism communicates with the outer world in three quite different ways: primarily via the *sense organs*, but also through *breathing* and through *limb activity*. On the other hand, it establishes its *specific physiological competency*, its independence [or autonomy relative to the world], chiefly through the *digestive organs*, but also through its relatively closed *circulatory system* and its almost wholly encapsulated *nerve center* (p. 23).

He immediately adds that the human organism "is as much a member of the surrounding world as it is an independent world of its own; and by mediating between these two kinds of existence, between its biological self and the surrounding world, it creates an active interplay between the two. It always gives the lie to any one-sided explanation of its reality, which we can approach only by adopting multiple perspectives" (pp. 23-24). So we find a unity of polar opposites, not only within the organism, but also between the organism and the world.

13. Figure 12.6 credit: Emöke Dénes, CC BY-SA 4.0.

14. Figure 12.7 credit: RedGazelle123, CC BY-SA 4.0.

15. Figure 12.8 credit: Charles J. Sharp CC BY-SA 4.0.

16. See Riegner 2008. Riegner's work on birds would take us too far afield to allow for coverage here. He has also written an important paper in the philosophy of biology, dealing with the "new archetypal biology and Goethe's dynamic typology as a model for contemporary evolutionary developmental biology" (Riegner 2013).

17. Schad goes on to remark on the second page: "My purpose is to place in the absolute center of inquiry the direct perception of the animals most closely related to us — the mammals — as they live in their natural environment. We shall approach them with the confidence that their lives openly and plainly convey what is essential for our understanding of them. As we recognize the unique quality of each animal form, it poses a much neglected question whose answer … can be supplied only by the living form of the animal itself".

Sources

Brady, Ronald H. (1987). "Form and Cause in Goethe's Morphology", in *Goethe and the Sciences: A Reappraisal*, edited by F. Amrine, F. J. Zucker, and H. Wheeler, pp. 257-300. Dordrecht, Holland: D. Reidel. Available in the Nature Institute's Ronald H. Brady Archive: https://www.natureinstitute.org/ronald-h-brady/form-and-cause-in-goethes-morphology

Brady, Ronald H. (1998). "The Idea in Nature: Rereading Goethe's Organics", in *Goethe's Way of Science: A Phenomenology of Nature*, edited by David Seamon and Arthur Zajonc, pp. 83-111. Albany NY: State University of New York Press.

Brady, Ronald (2006). “Direct Experience”, Chapter 1 in *Being on Earth: Practice in Tending the Appearances*, by Georg Maier, Ronald Brady, and Stephen Edelglass. Full text is available at https://www.natureinstitute.org/book/being-on-earth. Hardcopy book is available from Logos Verlag Berlin (2008): https://www.logos-verlag.de/cgi-bin/engbuchmid?isbn=1887&lng=eng&id=

Goethe, Johann Wolfgang von (1995). *Scientific Studies*, edited by Douglas Miller. Vol. 12 in Goethe: Collected Works. Princeton NJ: Princeton University Press.

Holdrege, Craig (2014). “Goethe and the Evolution of Science”, *In Context* #31 (spring), pp. 10-23. https://natureinstitute.org/article/craig-holdrege/goethe-and-the-evolution-of-science

Holdrege, Craig (2019). “A World of Dynamic Connections: A Commentary on Wolfgang Schad’s *Understanding Mammals*. *In Context* #41 (spring), p. 9. https://www.natureinstitute.org/s/In-Context-41.pdf

Holdrege, Craig (2021). “What Does It Mean To Be a Sloth?” https://natureinstitute.org/article/craig-holdrege/what-does-it-mean-to-be-a-sloth. This article, in slightly altered form, is a chapter in the 2021 book by Holdrege, *Seeing the Animal Whole — And Why It Matters*, pp. 19-40. Great Barrington MA: Lindisfarne.

Lockley, Martin G. (2007). “The Morphodynamics of Dinosaurs, Other Archosaurs, and Their Trackways: Holistic Insights into Relationships between Feet, Limbs, and the Whole Body”, SEPM Special Publication No. 88 (published by the Society for Sedimentary Geology), pp. 27-51.

Portmann, Adolf (1967). *Animal Forms and Patterns: A Study of the Appearance of Animals*, translated by Hella Czech. New York: Schocken.

Riegner, Mark F. (2008). “Parallel Evolution of Plumage Pattern and Coloration in Birds: Implications for Defining Avian Morphospace”, *The Condor* vol. 110, no. 4, pp. 599-614. doi:10.1525/cond.2008.8503

Riegner, Mark F. (2013). “Ancestor of the New Archetypal Biology: Goethe’s Dynamic Typology as a Model for Contemporary Evolutionary Developmental Biology”, *Studies in History and Philosophy of Biological and Biomedical Sciences* vol. 44, no. 4, Part B (December), pp. 735-44. http://doi.org/10.1016/j.shpsc.2013.05.019

Sachs, Joe (1998). *Aristotle’s Physics: A Guided Study*. New Brunswick NJ: Rutgers University Press. Originally published in 1995.

Schad, Wolfgang (1977). *Man and Mammals: Toward a Biology of Form*, translated by Carroll Scherer. Garden City NY: Waldorf Press.

Schad, Wolfgang (2020). *Threefoldness in Humans and Mammals: Toward a Biology of Form*. Harlemville NY: Adonis Press. This is a substantially revised and expanded, two-volume edition of Schad 1977. An early, limited printing of the expanded book (200 copies) was titled, “Understanding Mammals”.

Seamon, David (2020). "Book Note", review of Wolfgang Schad’s *Threefoldness in Humans and Mammals* (under the title of “Understanding Mammals”). *Environmental & Architectural Phenomenology* vol. 31, no. 1, p. 15.

CHAPTER 13

All Science Must Be Rooted in Experience

In previous chapters we have seen how organisms, as centered agents, present us with rich, narrative contexts — mortal performances that proceed, with characteristic expressiveness and intention, through the stages of a unique life drama qualitatively recognizable as belonging to a particular species. And yet, as we have also seen, a powerful urge drives biologists to ignore, as far as they can, every *living* feature of those performances. The aim is to employ strictly physical terms of description.

They ignore, for example, what it must really mean when they say that animals “strive” to maintain their life, or that a wound “heals” itself, or that an organism “adapts” to its environment, or that it “perceives” a threat and “responds” to it. (Physical objects in general — stones, clouds, and dust storms — do not strive, heal, adapt, perceive, or respond.) But it is all too easy for any scientist to side-step such meanings and analyze the organism’s story into lifeless sequences of precisely lawful molecular interactions. And since there appear to be no gaps in the molecular-level picture, the resulting explanations seem complete. Only the organism is missing.

In other words, seamless as they may be in their own impoverished terms, such explanations are not in fact complete. They miss the simply observed fact that molecular-level interactions in an organism are always caught up in, and governed by, the higher-level pattern of a life story. We always find ourselves watching the meaningful *coordination of causal processes in an extended narrative* — an end-directed coordination that cannot be explained by the processes being coordinated. This is why explanations that never move beyond physics and chemistry stop short of biology.

Non-living explanations do, however, have one advantage: they conveniently avoid all those troublesome words I use throughout this book in discussing organic contexts and life stories — words such as *intention* and *purposiveness*, *idea* and *thought*, *agency* and *end-directedness*, *interests* and *meaning*. Most biologists prefer to have nothing to do with such terms.[1]

One stumbling block associated with those words is that they evoke features of our own inner lives — our human *experience*. It is, of course, healthy to avoid an anthropomorphic projection of human experience upon other organisms, where it does not belong. But we, too, are organisms, and therefore we have no cause to ask, “Does living human awareness belong in our biological science?” Instead we can only ask, “*Where* does this awareness belong in our biological science?”

If we ignore the character of our own life and experience, can we fully understand a world that has been capable of producing *us*? How can we gain our scientific ideas, if they are not *empirical* — if they are not expressions of our most rigorously considered *experience*? And how can an evolutionist reasonably assume that our own experience has nothing at all in common with that of our evolutionary forebears?

Perhaps first of all we need to ask what is meant when we refer in this way to our own experience.

Two distinguishable but indivisible aspects of human experience

It is clear enough — trivially clear, it seems — that we cannot conceive any material phenomenon, or any reality at all, that is inconceivable. If an object or phenomenon did not lend itself to our conceptualizing — if its true nature could not be captured in thought — we would never know it because we would not even be able to think it. If we cannot conceive something, it cannot appear as a definite and coherent fact of our experience. Either the world's character is at least partly given in thought, or else it is alien to our understanding.

Some things are so obvious and foundational that we easily forget them in our quest for new knowledge. The fundamental role of thinking in all our understanding may be one such thing.

But our conceptualizing or thinking capacity is only one of the contributors to our experience, and therefore to an empirical science. Our senses also contribute. And here, too, we can say that, without the qualities of sense, we have no material world to talk about. If you open yourself to any phenomenon whatever and then (in imagination) remove all sensible qualities from it — all the given colors, sounds, touch sensations, smells, and so on — nothing will be left. You are confronting an absolute void.

Not even the most rigorous mathematics can give us a world, since nothing in mathematical thought itself tells us what the mathematics is about. We must *apply* the mathematics to sensible experience if we want to see how it is embodied in material reality. But the same applies to all thinking, not just to the purely quantitative ideas of mathematics: only by bringing our thought into relation with what comes through our senses do we find the world taking shape around us. This is a key idea that we will flesh out below.

There seems to be no basis for assigning priority either to our sensing or our thinking. These are two aspects of a single reality, and their separation in human experience is an aspect of the structure of our being as cognitive agents. This structure, we will see in Chapter 23, has changed over the course of human evolution.

For the moment, it is enough to ask ourselves: Do we have any knowledge of the material world that is not a marriage of sense and thought?[2] It will not require much work to realize that the answer is “No”.

Without relations of thought, we have only chaos

Many of us (especially as we grow older) have had the experience of “losing our bearings” while driving or riding in normally familiar territory. Suddenly a powerful sense of disorientation takes hold of us, and the entire landscape becomes a disconcerting question mark. For a moment we have no sense for where we are or where we are headed, so that our usual feeling of comfort with our surroundings is lost. The confusion that sets in, however short-lasting, is one of profound lostness. The connections linking where we are at the moment to a wider, coherent context have gone missing. The conceptual map through which we grasp the meaningful arrangement of the larger landscape is no longer anchored to our current location.

One might think that the problem here applies only to matters of spatial location. After all, when I become disoriented while driving, all the particular objects around me — houses, trees, road surfaces, animals — continue to make perfectly natural sense. My disorientation applies only to one aspect of my environment.

But the fact is that those other aspects also depend on the thinking that weaves parts into a meaningful whole — not only spatially, but also, for example, functionally.

Suppose I were to lose all conceptual grasp of the relations governing the scene outside the window where I am now writing — a scene with a white pine tree standing just a few meters beyond my desk. I would then have no more reason to connect the particular branch I am now looking at with the trunk of the tree than I would have for connecting it with the contiguous patch of blue sky. The idea that the sky is *up there* while the tree is *here*, or that the pressure of the wind against the branches is responsible for their waving, or that the roots in the ground provide mechanical strength in support of the tree’s uprightness, or that the entire tree as an integral unity is *growing* — these would no longer serve to hold the tree together in my understanding as the unitary kind of thing, or being, it really is.

A wholly unformed content of sense perception is something we presumably never experience as such — because it is not yet *experience*. It assumes meaningful, experiential form only so far as it is informed by thought. In routine perception, this informing is already accomplished before we are aware of it. Through long training, our senses are educated by our thinking, so that we do not need to reflect consciously, over and over again, upon familiar elements of our experience.

We can see this more clearly when we consider cases where the normal education of the senses has been partly lacking.

We do not see with our eyes alone

It can be hard for us to recognize all the thinking that is woven into our perceptual experience, much of it originating far back in childhood. But there are now well-studied cases where some aspects of the usual marriage of sense and thought never occurred in the first place — not until adulthood. I have in mind those individuals, born blind, who were much later given sight through operations.[3] Here, from a different angle, we find vivid evidence for the insufficiency of "mere" sense impressions, and for the role of thinking in giving us lucid, intelligible experience of the world.

The British neuropsychologist, R. L. Gregory, describes the case of "S.B.", who received donated corneas to replace his own congenitally opaque ones at age fifty-two. After the operation, the bandages were removed from his eyes, and

> he heard the voice of the surgeon. He turned to the voice, and saw nothing but a blur. He realised that this must be a face, because of the voice, but he could not see it. He did not suddenly see the world of objects as we do when we open our eyes.

He made progress while still in the hospital, but it all involved learning *how to understand what he was looking at* so as to bring it to coherent and meaningful form. He judged that he could hang from the window ledge of his room with his feet touching the ground when the distance was in fact at least ten times his own height. When, on the other hand, he had had previous touch experience with objects, he could estimate visual distances much more realistically.

S.B., like many such patients, found it stressful to adjust to his new powers of sight. For example, he had difficulty "in trusting and coming to use his vision when crossing a busy road":

> Before the operation he was undaunted by traffic. We were told that previously he would cross roads alone, holding his arm or his stick stubbornly before him, when the traffic would subside as the waters before Christ. But after the operation it took two of us, on either side, to force him across: he was terrified, as never before in his life.

Following his operation, S.B. fell into an increasingly deep depression. Making sense of things was hard work, and he would often prefer to encounter new objects with the familiar sense of touch alone. "Some of these people", Gregory writes, "revert very soon to living without light, making no attempt to see. S.B. would often not trouble to turn on the light in the evening, but would sit in darkness." Over time "he gradually gave up active living, and three years later he died." (Gregory 1978, pp. 193-98).

Such cases highlight for us the extent of work required to make rational sense of the unformed content supplied by our senses. This depends a great deal on the availability of relevant prior experience — that is, experience that results from already having made sense of prior perceptions. But the unnatural work of suddenly having to cope in adulthood with an overwhelming mass of unfamiliar sensations so as to find the connecting thoughts that form them into a coherent and satisfying picture can clearly prove exhausting.

How do things around us become what they are?

We have all been exposed to so-called ambiguous figures — images cunningly contrived like those of Figure 13.1 so that they can come to meaningful appearance with the aid of at least two altogether different and conflicting conceptions of their governing relations. While the “image on our retinas” remains the same, the way we *think* the image makes a huge difference in what we see.

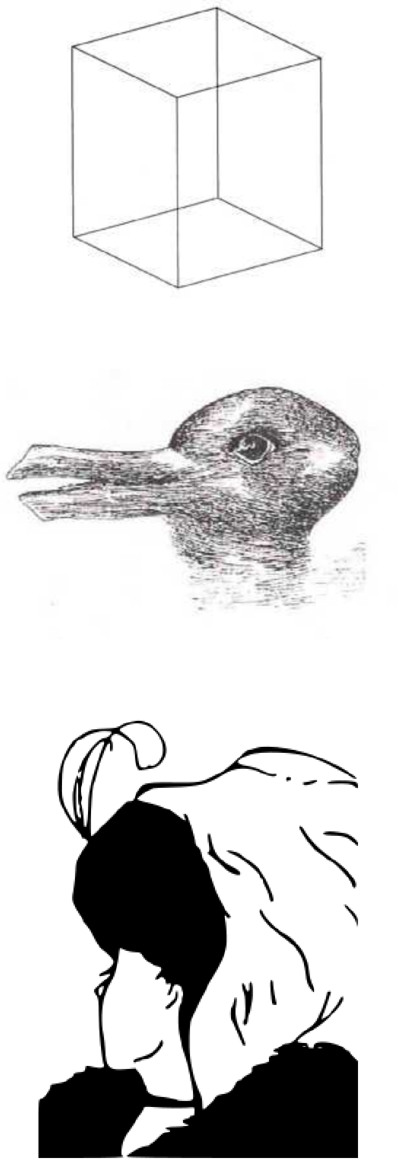

Figure 13.1. Three examples of ambiguous figures: Necker cube (above); a duck or rabbit (middle); young woman or old hag (below).

This usefully draws attention to how we must *participate with our thinking* in the appearance if in fact its potentials as an actual phenomenon are to be realized. However, the fact that the ambiguous figure allows different interpretations does not mean that the contribution of thought is arbitrary or merely subjective. If we try to think the Necker cube with the idea of a sphere, we will not come to a meaningful image. Our thoughts must be those already implicit in the sensible aspect of the appearance.

Ambiguous figures are an unusual case. What remains true even in the more general case of great art is that we can always deepen our thoughtful understanding of it. Anyone as artistically unaware as the present writer may have the experience of hearing an art historian lecture about a particular painting or a particular cultural tradition of painting, and then find that he looks at certain works with newly and refreshingly informed eyes. The picture he sees now is not the same one he saw before.

But this is true also of natural scenes. Confronted by a violent thunderstorm, Stone Age man did not actually *see* the same atmospheric phenomenon we see today. *Our* “art lecturer” in this case has been the scientist, whose conceptualizations have been assimilated by the entire culture of the last few hundred years. The lecture has ceaselessly entered our ears through the words and meanings we have learned from infancy onward. We see with the perceptual and conceptual resources of our own era. (As for Stone Age man and ourselves, it may be that we *both* miss important aspects of the thunderstorm. But that is a point for Chapter 23.)

I would be saying nothing unusual if I were to contend that we have no *theories* except by virtue of the thinking that constitutes them as what they are. It is a vastly more difficult matter, however, to realize, as we surely must, that we have no *things* to theorize about in the first place except by virtue of the thinking that constitutes them as the things they are. So if we are content merely to accept things as given, then before we even begin our scientific work, we have already committed ourselves to the particular, culturally influenced thoughts that bring to appearance the objects and phenomena currently available to our scientific curiosity.[4]

There remains the question, then: “How adequate are the thoughts through which our natural surroundings have gained whatever meaningful form they now have for us?” Every bit of nature can be seen more or less profoundly, with deep insight or a superficial glance; with an intense, trained perception, or a lazy attention that merely glides over surfaces; with loving, qualitative detail or with remote abstraction. We may not easily misconceive a cube as a sphere, but we *can* be content to see far less of the world than is actually available to a more penetrating vision. From force of habit we of the past few centuries may, for example, see merely “mindless objects”, despite the fact that it is our own, culturally informed minds through which the objects come to the only appearance we are given.

Recognizing the element of our own thinking in the data of science would seem to be a prerequisite for any rigorous scientific understanding.

Do we really want an empirical science?

The fact that thinking is already present in the only phenomena available to scientific investigation is one of those fundamental truths, easily recognized yet widely ignored, that can change everything. It tells us something about how intimately we as thinking beings are woven into the universe that brought us, along with our thinking, into existence. Or, in the lower-level (molecular) context of the preceding chapters: it reminds us how intimately the world’s wisdom has been woven into the directed activity through which our bodies, including our brains, have been formed (Chapter 8).

But, important as thinking is, it cannot by itself give us a world. There is also the “something” that thinking illuminates — the unformed contents provided by our senses. If, as we saw above, our senses cannot give us identifiable or nameable or recognizable *things* without first being informed by thinking, neither can thinking give us any such *things* without there first existing a sensible content capable of being so informed.

A new kind of attention to the senses was the glory of the Scientific Revolution — a revolution that was in part a reaction against the untethered intellectual flights of the medieval doctors. The pioneers of modern science sought to bring their thinking into disciplined connection with careful observation and manipulation of the world around them. Thus was born the ideal of an *empirical* science — a science of practical experience rather than speculation. To this day the ideal remains sacrosanct among scientists.

But here a curious contradiction emerges. For, the ideal is directly belied by an entrenched conviction (elaborated in the following section) that human sense experience is irreducibly subjective and illusory. If this is true, how is an empirical science supposed to give us an objective understanding of the world? Doubt on this score has been met by an ever greater reliance on the extremely thin “experience” of instrument dials, gauges, and read-outs.

The idea behind this reliance is that the quantitative rigor and sensitivity of the instruments can compensate for the limitations of the human senses. But whatever those limitations might be, the senses are what give us access to the world. Numbers are not material entities. They are conceptual, and the fact remains that thinking alone — including, as I have already indicated, mathematical thinking — cannot give us a world. We must *apply* the mathematics to sensible experience if we want it to tell us something about material reality. Where are we to gain that experience (so as to have actual things to talk scientifically *about*), if not through our supposedly unreliable senses?

Our contradictory attitude toward human experience — hailing it as the foundation of any true science, while denigrating it as the source of confusing subjectivity — has long been an open wound in the body of science. Yet the issue is rarely given thought by the working scientist. Philosophers, meanwhile, continue picking at the wound as they have for the past few centuries, to little avail.

Nevertheless, the entire problem, having been falsely posed, can be simply resolved.

It is careless thought that deceives us, not our senses

Who has not heard the various clichés about how our senses “lie” to us. Try immersing one hand in a bowl of hot water, and the other in a bowl of crushed ice, holding them there for a while. Then remove them both and place them together in lukewarm water. Initially, one hand will feel the water as cool and the other as warm. So goes the “proof” that the felt qualities of things are subjective and misleading compared to the objective report of a thermometer.

The conclusion is wrong. If you follow an identical procedure with two thermometers, you get a similar result: the two columns of mercury initially show different temperatures. Over time they move in opposite directions until, as happens with our hands, equilibrium is reached. Nor does hand or thermometer offer false reports during the period of adjustment. At every moment the reading correctly reflects the changing *relations* between water and measuring instrument. Such relations must be grasped in thought, which is the only way we ever make sense of our senses.

How many school children have been given an experience of these bowls of water! And how many have learned the lesson that their experience is worthless and deceptive! All the better, I suppose, to prepare them for further misconceptions of the sort we will now consider.

Earth and sun

Another classic example of our “lying” senses has to do with an appearance we witness every day: it *looks*, we are told, as if the sun goes around the earth, not as if the earth is rotating. In his play, *Jumpers*, Tom Stoppard skewered this particular claim by having one of his characters ask: "Well, what would it have looked like if it had looked as if the earth was rotating?"

Surely it *should* look exactly as it *does* look; any other appearance would have been false to the fact of rotation. It’s just that we have to employ our thinking in order to make sense of *any* appearance. Once we grasp this truth, we cannot help realizing how wrong it is to declare the appearances from earth to be false. We are free to take up any vantage point we choose. Copernicus chose to look, in imagination, from the vantage point of the sun. This was a decisively important step. But surely we have no more right to absolutize that perspective than we do the one from earth. The heliocentric view is as "parochial" as the geocentric view compared, say, to a galactocentric view, where observations over time would make it clear that neither the earth nor the sun *circles* the other.

Scientists, in their research, do in fact routinely employ purely local coordinate systems for their immediate purposes wherever they happen to be on earth. It would make no sense to use a heliocentric coordinate system when mapping out the placement of plants in an experimental garden. And neither scientists nor the rest of us have any particular difficulty holding all the various possible perspectives harmoniously together. When standing in a group around a tree, we all perceive the same tree, even if no two of us see exactly the “same” image of it. Our senses must be informed by our thinking. Only then does a coherent appearance — as opposed to a chaotic aggregation of disconnected sense impressions — present itself.

The atom and beyond

Here is another scientifically sanctioned “old wives’ tale”, taken from a PBS television special written by science journalist, Timothy Ferris:

> The baseball and the bat are mostly empty space. Their solidity is an illusion created by the electromagnetic force field that binds their atoms together … We credit the home run to the batter, but the fundamental force responsible is electromagnetism (Ferris 1985).

The picture we are invited to contemplate is one of atoms. Each atom consists of minuscule particles packed into an infinitesimally small nucleus. Added to these are even more minute electrons traversing enormous tracts of empty space as they orbit the nucleus at a vast distance. It is, we are told, the electromagnetic force binding the electrons to the atomic nucleus that deludes us into losing sight of all that empty space comprising nearly the whole of the individual atom, and therefore also nearly the whole of the bat and ball.

But notice: “empty space” gains meaning here only when we picture the nucleus and the orbiting electrons as a collection of nicely solid particles — solid like little space-occupying bits of the actually experienced world. We are then supposed to contrast these particles in our minds with the great expanses occupied by no particles at all.

But this is the picture that physicists labored throughout much of the twentieth-century to eradicate from our imaginations. For good reason: they well know that the erstwhile “particles” of atomic theory do not exist — not as bits of material stuff we can contrast with empty space, nor even as the “wave-packets” that are sometimes substituted in speech for the particles. The only *material stuff* we are given in the universe is the sensible content of our perception.[5]

Look at what is happening here. Ferris is trying to get us to doubt our perception of the material world. Yet he is doing so by asking us to imagine little bits of material stuff in the imperceptible atom. So, rather than discrediting our perception, he is in fact illustrating the impossibility of imagining a world without the contents of perception. The only illusion is on his part: he is projecting the contents of perception into a theory-laden, falsely imagined, submicroscopic realm where in fact no perceptible content is given to us.

To reinforce the point, listen to neuroscientist and philosopher, Paul Churchland, assuring us that our various forms of observation — sight, hearing, touch, and so on — are not to be trusted:

> The red surface of an apple does not *look* like a matrix of molecules reflecting photons at certain critical wavelengths, but that is what it is (Churchland 1988, p. 15).

Our senses, in other words, are said to fail us because they do not show us the red surface of the apple as *really* consisting of unimaginably small “billiard balls” or “wave packets” reflecting each other and being reflected. And so, again, apart from such sense-based imagery — the very thing that physics today forbids us from projecting into atomic theory — Churchland’s argument would be wholly unpersuasive.

The point is decisive, and bears repeating. Only by picturing particles (or waves) as little bits of the qualitatively experienced world can the reader fill in Churchland’s description in a way that makes it sound meaningful. But this sensible perception of the world’s qualities is exactly what Churchland is trying to dismiss. While telling us that the familiar qualities of the world are illusions, he invites us to project these same qualities into the sub-microscopic realm. That realm then becomes proof that the familiar qualities aren’t to be taken seriously. Apparently sensory qualities, such as the firmness and solidity of small bits of reflectable matter, are illusions *here* (where we can experience them), but real *there* (where we cannot).[6]

The moral of the story? Even when we are trying to talk about a world without the qualities of our senses, we end up talking about the qualities of our senses — but in a nonsensical way.

Our “missing” bat sense

One last example. Those who disparage our experience love to point to creatures who perceive things we cannot. Wouldn’t we live in a different reality if, say, we had the infrared vision of some snakes or the “sonar” (echolocation) sense of a bat? Of course we would — but only in the way those who are deaf or blind would live in a different reality if their senses were unimpaired. Perhaps the most striking thing about our perceptual worlds is their continuity and coherence, despite the supposedly discrete nature of the sense data and of the different senses themselves. Adding a new sense gives us a richer picture, but it is a richer picture of the unified world we already know.

We heard above in the case of S.B. that it can be difficult, as an adult, to cope with an overwhelming content of sense perception through organs of sense that have not, in the normal course of things, already been educated by thinking. But the fact remains that the normal course of education presents no particular difficulty at all.

If the bat’s echolocation were suddenly and miraculously added to our own array of senses, we would presumably suffer some disorientation just as S.B. did when the bandages were removed from his eyes. Like all our other senses, our new sense would need to be educated by our thinking. But we would have no reason to think that our new world stood in contradiction to our previous experience.

Nor is there any reason to think that a person naturally born with a capacity for echolocation would find his world *conflicting* with that of the rest of us. The two worlds would certainly vary in the richness of the contributions made by the different senses, but they would no more disagree with each other than the truly vast difference between the most sensitive musician’s ear and the dullest, least attentive ear among the rest of us would spell a disagreement of sense perception.

To believe that we can truly know the world is not to believe that our present knowledge is exhaustive, or that the world cannot present itself within many modes of consciousness, or that our present powers of perception cannot be deepened beyond anything we can now imagine.

One reason we can be confident that newly developed senses — whether those of a bat or otherwise — would harmonize perfectly with our previously existing senses is that the harmony does not depend on unformed sensory content. It seems safe to say that the education of our senses by thinking is essential to the unity of our experience of the world. Thinking has the quality that all thoughts can enter into harmonious relation with all other thoughts. The thought-world knows nothing of absolute discontinuity.

The world of thought is, in a profound sense, *one*, and this is what enables us to have *one tree* despite the fact that we view the tree from many sides and never have two identical visual impressions of it. This unity of the thought-world also explains how it can be that in any text or speech, individual words can be informed by their context. Their meanings are shaped by the thought of the context as if they were essentially of one substance with it. They merge their own identity into the integral and coherent unity of the whole.

Even the recognition of a logical contradiction requires a perspective wherein we can see particular thoughts joined together by a relation of sameness as well as significant difference. There can be no *absolute* opposites, for if they had nothing at all in common, there would be no way for us to think them together in order to compare them or pronounce them “opposite”. We can have contrary things to say only about ideas participating in a common realm of meaning.

Closing thoughts

The contents of our senses — if we could somehow know them before they are illuminated and given form by thinking — could not possibly lie to us. They are just not in the business of being either true or false. In fact, as we have seen above, they are not even *there* in any meaningful sense until the illumination by thinking has occurred. Whatever it is that comes through the senses apart from thinking — and how could we name it without bringing concepts to bear, after which it would be *more* than what comes through the senses alone — can only be an unformed potential. Such potential cannot be true or false. Only our thinking can be adequate or inadequate, misleading or helpful, true or false — depending on how surely it brings to consistent and reliable appearance whatever potentials have been presented to our senses.

Perhaps the first and most naive reaction to all the foregoing is the complaint, “You seem to be saying that everything is ‘just in my head’, which can hardly be true. In the depths of the deepest ocean trench, or on the backside of the moon, there are solid things and real processes that no person is now experiencing, and yet we can be quite sure that they continue on quite heedless of our disregard.”

But this objection reflects habits of thought so obdurate that they recoil even from a basic recognition of what is being proposed. After all, the assumption that thinking and the qualities of things are all “just in our heads” is exactly what I have been disputing. The point is that thinking and the qualities of things are not merely in our heads, but are also *there*, in the world to which we must conform our own thinking — the only world we could ever know. The world itself exhibits the nature of living experience, and the way in which we are invited to participate in it is not altogether different from the way we are invited to participate in the experience of another human being. The question is whether we are open to the world’s meaningful gesturings, or have simply lost all interest in what speaks to us from our surroundings.

We need to reckon with the intense and tyrannical grip of old habits of thinking. As the philologist Owen Barfield has reminded us, for most people living before, say, the sixteenth century the proposition that thoughts are “things” isolated in our individual heads would have been difficult or impossible to comprehend — just as difficult and impossible to comprehend as is, for us, the proposition that thoughts belong to and inform the stuff of the world (Barfield 1967, p. 45).

For the student of the evolution of consciousness (Chapter 23), the question is not, “How can anyone arrive at the ‘crazy’ idea that thinking belongs to the warp and woof of the world?” but rather, “How did it happen, in this last brief, historical moment, that we have come, ‘crazily’, to doubt a world humming with the high tension of creative thought?”

WHERE ARE WE NOW?

Is Our Way of Knowing the World Truly Revelatory?

Biologists have studiously applied themselves to continual reinforcement of a materialist attitude that aims to ignore everything *living* about organisms. And this attitude is most intense when it comes to ignoring the reality of human experience — human interiority — through which alone we can have an empirical science. It all makes for a science that is extraordinarily inattentive to the ground upon which it stands.

It's a strange thing, and (as I have tried to show in this chapter) has led to all sorts of self-contradictory claims about the uselessness of direct human experience for science. We have considered arguments such as, "It doesn't look as though the earth rotates on its axis and revolves around the sun"; or "Putting our hands in separate bowls of cold and hot water, and then putting them both in a bowl of tepid water proves the fallibility of our sense for warmth"; or "The red surface of an apple does not *look* like a matrix of molecules reflecting photons at certain critical wavelengths, but that is what it is" (Paul Churchland).

The proper conclusion is that our senses, considered by themselves (and it takes some critical work to consider them that way) *never* lie to us. They're not in the business of being true or false; they just are what they are. Truth and falsehood are features of thinking, not of the raw givenness of sense. They apply only to the thinking that, joined to the reports of our senses, brings the world to more or less coherent and revealing appearance.

Humans belong to the world, are nurtured by the world, and are naturally given means to know the world in which we are so intimately immersed and from which our own substance and capacities are derived.

Putting it in slightly different terms: If we really believe that we can know the world (as virtually everyone does), we must believe that, by nature, it lends itself to our understanding. It "speaks" to us in the language of our own experience, which is to say that its native language is also our language. The language of the world's expression is the language of our experience.

In Chapter 23 ("The Evolution of Consciousness") we will look at the powerful historical evidence grounding this understanding of the relation between the world's speaking and our own speaking. And in Chapter 24 ("How the World Lends Itself to Our Knowing") I will attempt to carry the considerations of this present chapter as far toward a conclusion as I can.

Notes

1. There is also the phenomenon I have referred to as biological blindsight. Biologists certainly do recognize an end-directed coordination of events in organisms. They want to understand how cells, by means of almost unthinkably complex organizational activity, prepare for and go through cell division. Or how predators strategically mobilize all their physical resources in order to capture prey. It's just that the *explanations* for such coordinated activities are, for artificial reasons, required to consist, at bottom, of causal processes that make no reference to the fact of higher-level coordination.

2. I take the phrase, "marriage of sense and thought", from a wonderful book of that title (Edelglass et al. 1997).

3. The classic study is that of M. von Senden. See also the discussion of "S.B." in Gregory 1978 and that of "Virgil" in Sacks 1995.

4. Anyone who would like a fuller exposition of the role of thought in what we perceive might want to read the three chapters by philosopher Ronald Brady in the freely available online book, *Being on Earth: Practice In Tending the Appearances*. For the fact that "culturally influenced" does not mean "*merely* cultural", see Chapter 23.

5. If you wanted to speak in terms of physics, you would have to talk about forces *entirely filling* the space of the atom (and extending far beyond it). Such forces can be measured, but bits of "stuff" are *never* seen. The "pictures of atoms" we are sometimes shown are in fact graphs — for example, graphs of measured forces. And if the space of the atom is wholly permeated with forces, *that* fact gives us no basis for contrasting substantive particles with empty space. It merely shows that particle physicists have abstracted their understanding so far from the perceptible world that their theoretical constructs do not refer to anything like familiar elements of experience. These constructs are undoubtedly rooted in meaningful structure at the submicroscopic level — structure such as that given in the pattern of forces — but this is not yet to be speaking about *things* in the sense of material reality. As I try to show in Chapter 24, such *things* are products of the "marriage of sense and thought". Without both of these together, nothing is *there* for us.

6. Physicists, having learned long ago not to assert the existence of real particles and waves in the sub-microscopic realm, came to speak instead of mathematical probabilities corresponding to various instrumental read-outs. What material reality these probabilities correspond to cannot be meaningfully discussed. And this should be no surprise, given that the only reality we have is a reality of *experience*. Talking about contents of experience that we cannot actually experience leads to gibberish.

Sources

Barfield, Owen (1967). *Speaker's Meaning.* Middletown CT: Wesleyan University Press.

Churchland, Paul (1988). *Matter and Consciousness*. Cambridge MA: MIT Press.

Edelglass, Stephen, Georg Maier, Hans Gebert and John Davy (1997). *The Marriage of Sense and Thought: Imaginative Participation in Science*. Hudson, NY: Lindisfarne.

Ferris, Timothy (1985). *The Creation of the Universe*, PBS television special.

Gregory, Richard L. (1978). *Eye and Brain: The Psychology of Seeing*, 5th edition. New York: McGraw-Hill.

Maier, Georg, Ronald Brady and Stephen Edelglass (2006). *Being on Earth: Practice In Tending the Appearances*. Full text is available at https://www.natureinstitute.org/book/being-on-earth. Hardcopy book is available from Logos Verlag Berlin (2008): https://www.logos-verlag.de/cgi-bin/engbuchmid?isbn=1887&lng=eng&id=

Sacks, Oliver (1995). “An Anthropologist on Mars: Seven Paradoxical Tales”. Vancouver WA: Vintage Books.

Talbott, Stephen L. (1995). *The Future Does Not Compute*. Sebastopol CA: O’Reilly and Associates. Full text available at https://netfuture.org/fdnc/.

von Senden, M. (1960). *Space and Sight: The Perception of Space and Shape in the Congenitally Blind Before and After Operation*. London: Methuen.

Chapter 14

How Our Genes Come to Expression

(It Takes an Epigenetic Village)

If your understanding of genetics comes from your newspaper's science section, or a popular science magazine, or any other source intended for the general public, then you will not have been given the remotest glimpse of what actually goes on with the genes in our bodies. In fact, geneticists themselves have been known to lament how limited their knowledge of gene-related activity is, simply because the demands of professional specialization scarcely allow a wide field of view.

But it turns out that a wide field of view is the one critical prerequisite for any adequate understanding of genes. Only a broad survey can illustrate how every gene, like a significant word in a text, receives its full meaning only through the interweaving and converging influences issuing from all the elements of its context.

My aim here is to offer such a wider, "epigenetic" view — and to do so in the briefest space possible. If I succeed, you will begin to sense a biological landscape that reconfigures many long-standing assumptions, not only about genetics itself, but also about the character of all living activity.

High expectations: the promise of molecular biology

After the discovery of the structure of the DNA double helix in 1953 and the elaboration of the "genetic code" during the early 1960s, the *expression* of a gene was thought of as the production of a functional protein corresponding precisely to *instructions* in the gene — instructions that were spelled out in the gene's *sequence* of DNA "letters", or *nucleotide bases*. The protein's production, based on this sequence, was routinely described as a cut-and-dried, fully determined, rather mechanistic affair. The larger picture was sometimes summed up in this formula:

`DNA makes RNA, RNA makes protein, and protein makes the organism.`

A few key terms may help to flesh out the formula as it was then understood. (All the special vocabulary is elaborated in an online glossary at https://bwo.life/mqual/glossary.htm.)

The first step in gene expression was thought to be the binding of a protein *transcription factor* (one of many such factors existing in the cell) to DNA at or near a target gene. This led to the adjacent binding of a complex protein called *RNA polymerase* (often described as a "molecular machine"), which then *transcribed* the DNA sequence of the gene into an RNA molecule closely mirroring the DNA sequence.

Finally, the RNA was exported from the cell nucleus into the cytoplasm, where it was *translated* into a specific protein. The translation was carried out by another complex “molecular machine”, this one composed of both protein and RNA and known as a *ribosome*. The sequence of amino acids in the resultant protein was said to have been *coded for* by the sequence of nucleotide bases in the gene. A parallel was sometimes drawn with Morse code, in which a sequence of dots and dashes codes for a sequence of alphabetic letters.

The discovery of the entire scheme, which seemed so neat and tidy, was almost universally welcomed.

But there was already a curiosity. Consider the picture. The production of a protein from DNA was initiated by a protein transcription factor. The “molecular machines” doing the work of transcription and translation consisted, in whole or in part, of proteins. Moreover, it was recognized that proteins were decisive for the very existence of DNA, as well as its replication, maintenance, and repair. So not only were proteins required in order to explain their own synthesis, but they were also required in order to explain the existence of DNA.[1] At the same time, DNA was clearly required for the existence of proteins.

You might think the chicken-and-egg problem here would have given the scientific community pause during its single-minded, twentieth-century rush toward a gene-centered view of life. Was it really genes that made the organism, including its proteins? Or was it proteins that made the organism, including its genes? Or were both points of view terribly flawed and unbiological, so that we were being asked to rise to a more living and integral level of understanding where it is impossible to say that one thing unambiguously “causes” another?

Complications

Fast forward to today, and consider just one of the terms mentioned above: “transcription factor”. A riddle posed by many such protein factors involves their “promiscuous binding”. Transcription factors, of which there are over a thousand in the human genome, are not targeted to specific DNA sequences by some iron necessity. Most of them are quite capable of binding at thousands of locations throughout the genome — that is, at far more loci than they are actually found at in typical assays of living cells. In other words, we have to look for much more than a definitive, sequence-based targeting logic if we want to understand how transcription factors activate (or inhibit) specific genes in this or that specific kind of cell and context.

So the question arises, How does a transcription factor “know” which gene or genes to interact with? If its specificity — its ability to bind where it is needed — is not dictated by a simple and determinative match between its own binding domain and the DNA sequence it binds to, then how do we make sense of its well-directed activity? Is this activity merely expressing something like the logic at work in a humanly devised mechanism? Or is it more like a living language, where each word has expressive potentials that are in part lent to them by their context?

The answer — or, rather, the many answers — are still unfolding today. The one indisputable truth is that it takes a molecular “village” — a vigorous and entire cellular context —

to establish the correct and ever-changing relations between a transcription factor and the genes it helps bring to expression. The old idea that the relations among transcription factors, genes, and gene products are unambiguous — are governed by a fixed, necessary, and easily comprehended logic — is no longer tenable.[2]

Transcription factors and DNA engage in a complex play of form

To begin with, not just the DNA sequence, but also the moment-by-moment sculptural form, or conformation, of a DNA locus affects the binding potential of a transcription factor. This dynamically imposed form reflects the cellular environment. Also decisive are the plastic conformational potentials of the transcription factor itself. And then there are the many other essential molecules (”co-factors”) that may not even have the ability to bind to DNA, but which are nevertheless essential co-participants, along with transcription factors, in an interactive community through which a gene, or set of genes, is made ready for transcription.

For example, one way a transcription factor can contribute to the expression of a gene is by bending a short stretch of DNA into a shape conducing to further interaction. (For a striking illustration of this, see Figure 14.5 below.) By this means the initial presence of a transcription factor can make it easier than it would otherwise be for a second protein to bind nearby. In the case of one gene relating to the production of interferon (an important constituent of the immune system), “eight proteins modulate [DNA] binding site conformation and thereby stabilize cooperative assembly” (Moretti et al. 2008).

And so, despite the fact that “DNA is often mistakenly viewed as an inert lattice” onto which proteins bind in a sequence-specific way (Chaires 2008), the fact of the matter is altogether different. Proteins and DNA are caught up in a continual conversation of mutual influence and shifting form. It becomes obvious, then, that “No simple code combines all the various determinants of transcription factor binding specificity” (Slattery et al. 2014).

In other words, a transcription factor’s “recognition” of a DNA binding site is not a digital, yes-or-no matter, but a community judgment. And how could it be otherwise, given that no cell in our bodies (and no collection of molecules) lives merely for itself? Our activities always involve vast, cooperating communities of various sorts. Every cell and cellular organelle is caught up in a larger context of meaning and must be capable of adapting itself to, and supporting, virtually any of the infinitely varying activities we find ourselves engaging in.

A living flexibility is therefore crucial. So it is no surprise when one pair of researchers, studying a group of transcription factors in the genomes of animals, report “a dazzling array of strategies employed by [these] transcription factors to control gene expression.” The “emerging, unifying theme”, they say, is the ability of these transcription factors “to interact with many diverse partners. This high connectivity is probably crucial to assemble highly context-specific, transcriptionally active complexes at selected sites in the genome” (Bobola and Merabet 2017).

Genes and proteins interact in tangled causal webs

It is hard to take in the full significance of this "high connectivity", which is typical of so many biological processes. One way to visualize the complications is to consider the fact that some transcription factors can target genes for other transcription factors. And, of course, this second group of transcription factors might target the genes for still other transcription factors as well as the genes or regulatory sequences associated with the first group. We can easily imagine the tangled causal webs resulting from this kind of inter-connectivity, where causal "arrows" can eventually circle back to their starting point. Unsurprisingly, there are entire fields of research today given over to complex gene and regulatory networks such as this one:

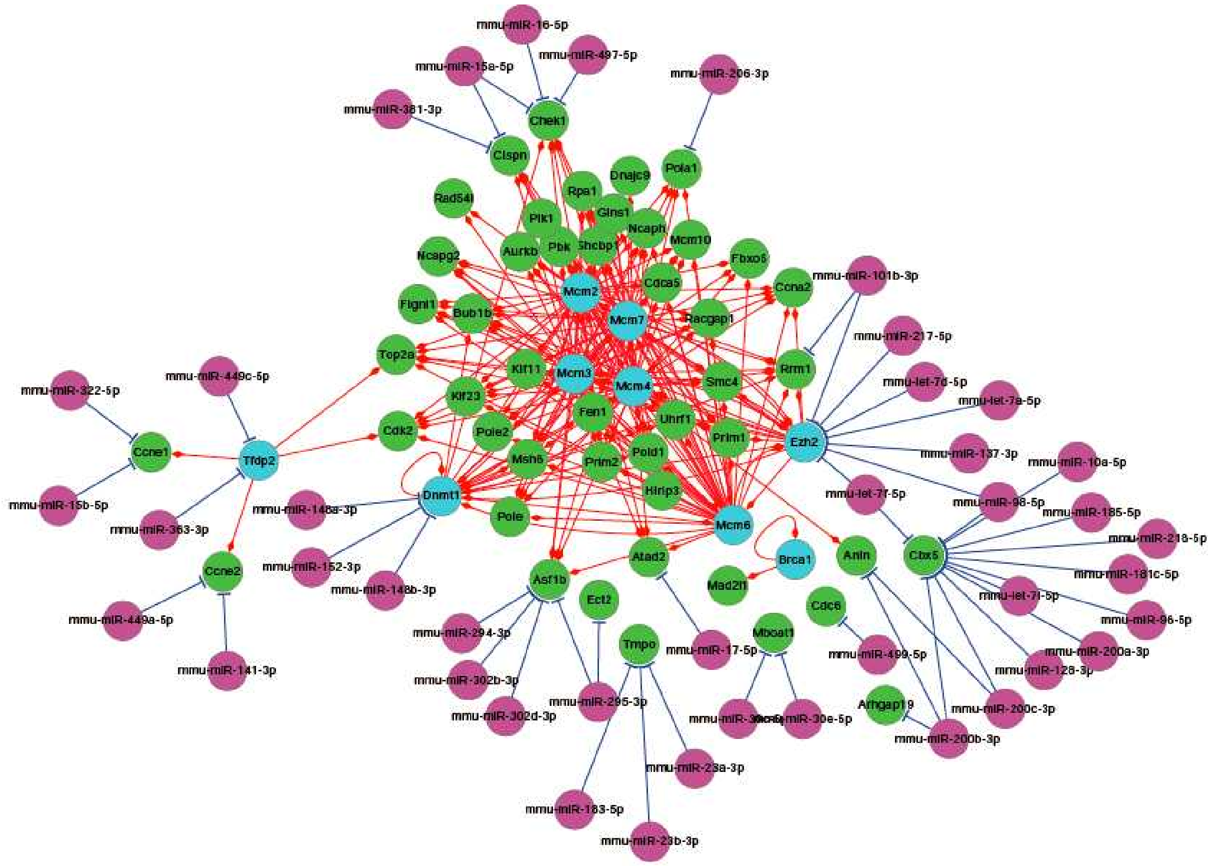

Figure 14.1. A modest regulatory network showing interactions among a cluster of transcription factors (blue), genes (green), and microRNAs (miRNAs — purple) under specific conditions in certain mouse immune cells. (We will discuss microRNAs below.) Red lines indicate regulation of transcription. Blue lines indicate just one sort of post-transcriptional regulation — that is, regulation of RNAs once they have been transcribed. Only selected relationships are shown; for example, the complex regulation of microRNAs (as opposed to their regulation of other molecules) is omitted from the diagram.[3]

Returning to the puzzle of transcription factor "promiscuity": this word reflects neither undisciplined profligacy nor uncertainty of function. Rather, it points to the unbounded, context-specific potentials of transcription factors. Their contribution to essential cellular processes, after all, is properly focused and far from promiscuous. They are caught up within a wisdom that seems to “know” exactly what it is doing. It’s just that this doing is complex and *living* — flexible and adaptive — far beyond what a simple, definitive, one-dimensional mapping between DNA sequence and a rigidly complementary protein shape would allow. This flexibility is what allows community-tuned activity in the larger surround to influence local goings-on in endlessly nuanced ways — all so as to satisfy the needs of the current context.

It is important to underscore here a fact we have found ourselves coming up against throughout this book: the tangled causal web we discover in organisms is not merely a matter of complexity. There are many nonliving physical contexts so complex that, as a practical matter, we cannot easily trace precise lines of cause and effect. This is true of eddies in a great river or in the atmosphere, and it is even true of some kinds of computer program. And yet no one would doubt in these cases that the relevant causes *could* be traced, at least in principle, or that the tracing would give us what is considered to be a full accounting of what we were looking at.

But, as I began explaining in Chapter 2, the purposive behaviors of organisms exhibit a kind of coherence and meaning that is not satisfactorily explained when we look only at principles of physical causation. The “causal confusion” in the organism’s case is not due merely to the complexity of the physical relations, but rather to the fact that explanation must be found at a “higher” level than physical lawfulness. The significance of what is going on is recognized only when we consider the insistent coordinating principles through which physical events are made to serve the needs and interests of organisms. Because concepts such as “need” and “interest” are incommensurable with the accepted principles of physical explanation, they demand recognition as explanatory principles in their own right.

The cell holds DNA in an intimate and instructive embrace

Our brief discussion of genes and transcription factors has, so far, been hopelessly simplistic. The chromosomes in our cells do not consist of a naked DNA double helix sporadically bound at particular sequences by this or that transcription factor. The picture is wholly different. Our DNA is intimately bound up with a massive, intricate, and dynamic protein-RNA-small molecule complex that, together with the DNA, is called *chromatin*. “Chromatin”, in other words, can pass as simply a name for the full substance of chromosomes. The proteins in this complex are as weighty as the DNA itself — and much more active and directive when it comes to gene expression.

Some of the protein constituents of this chromosomal substance — both the longer-term and the many transient constituents — can bind directly to DNA, thereby facilitating, blocking, or modifying the transcription of this or that gene. But other elements of chromatin, while not directly bound to DNA, nevertheless contribute crucially to the regulation of gene expression. Overall, the molecular factors associated with chromatin play roles such as the following:

- they help to condense or decondense the packing of the DNA (more tightly condensed DNA tends to be less accessible to activating factors);

- they move chromosomes or parts of chromosomes to different regions of the cell nucleus (the interior of the nucleus tends to be more transcriptionally active than the periphery);
- they attach parts of chromosomes to the nuclear envelope (many factors at or near the envelope bear on gene expression);
- they interweave and (almost miraculously, it might seem) disentangle chromosomes, while also forming decisively important chromosome loops (such as those we heard about in Chapter 3), — all so as to form various-sized “communities” of functionally related chromosomal loci;
- they loosen the two strands of the double helix in some places and twist them more tightly in others, which can make the difference between a gene’s accessibility or inaccessibility to transcription factors;
- they alter the electrical characteristics of particular loci (yet another feature bearing on the expression of affected genes);
- and so on almost without end.

As you may surmise, then, it’s not as if the power to determine gene expression outcomes is one-sidedly delegated to any genetic sequences, any transcription factors, or any other entities. It is rather as if the result arises in the way a musical performance is evoked from a jazz orchestra. A distinct locus of DNA certainly offers its own expressive potentials, but there is no telling — no predicting solely from an analysis of the sketchy DNA “musical score” — how the locus may be employed within the improvised, multi-cellular performance leading from a single fertilized egg cell to the mature human being.

But perhaps we would do better to imagine an exquisitely detailed, never-ending, self-assured, yet highly improvisational dance involving billions of molecular dancers within a cell — all coordinated with the choreography in neighboring cells and with the ongoing story of the organism as a whole. The performance, involving the fluid identity of countless players, is a long way from that of calculating or information-processing hardware.

In any case, the present point is that our DNA is thoroughly “wedded” to — bound together with — an almost unfathomably intricate arrangement of protein and RNA.[4] The protein and RNA constituents of this chromatin complex are fully as “information-rich” as the DNA. Genes, as such, cannot *do* anything, and certainly cannot transcribe themselves. The doing is in large part a function of the associated proteins, which, among other things, thereby participate in their own genesis. Alongside them are many other molecules, including water molecules (Chapter 5), all of whom give collective expression to the purposive coherence of the cell as a whole.

I have so far offered only a rather vague and general description of the highly effective embrace in which DNA is held. In later sections we will look further at some of its key features.

Getting started is hard to do

Meanwhile, leaping tall edifices of thought in a single bound, we will pass over the question how cells “know” which genes need to be expressed within the current context of a person’s activity and within the virtually infinite number of uniquely performing cellular niches within our bodies. We will also avoid asking how any single cell — which can play only a spatially minute part within an organ such as the liver or within a process such as wound healing — finds its own proper role in whatever the current larger performance happens to be. And so, assuming all the necessary contextualization and direction to be somehow wisely taken care of,[5] we will imagine just one cell embarking on a single task: to give expression to one among its 21,000 or so genes. How might this cell proceed?

Our imaginative exercise will necessarily be more than a little artificial. That’s because we need to think one thing at a time, whereas in the cell countless mutually entangled things are all happening at once. But we will try to make the best of it.

You may recall from Chapter 3 that packing DNA into a typical human cell nucleus is like packing about 24 miles of very thin, double-stranded string into a tennis ball, with the string divided into 46 separate pieces, corresponding to our 46 chromosomes.

To locate a modest-sized protein-coding gene within all that DNA is like homing in on a half-inch stretch within those 24 miles.[6] Or, rather, two relevant half-inch stretches located on different pieces of string, since most of our cells have two copies of any given gene, residing on different chromosomes. Except that sometimes one copy differs from the other and one version is not supposed to be expressed, or one version needs to be expressed more than the other, or the product of one needs to be modified relative to the other. So part of the job may be to distinguish one of those half-inch stretches from the other, and to act differently in the two cases. “Decisions” everywhere, it seems.

As a functional unit, a gene must participate in a performance appropriate to its context, and the highly distributed activity responsible for its function must be cobbled together by the cell according to the needs of the moment. There is no *predefined* path to follow once the cell has located the “right” half inch or so of “string”, or once it has done whatever is necessary to bring that locus into proper relation with other chromosomal loci participating in, and essential to, a joint performance.

One issue has to do with the fact that there are two strands of the double helix, and (in a chemical sense) these complementary strands “point” in opposite directions. In humans, protein-coding sequences can occur on both strands. Likewise, transcription (of both protein-coding and regulatory sequences) occurs on both strands, which is to say that the transcribing enzyme (RNA polymerase) can move in either direction along the double helix. The direction chosen — that is, the strand along which the RNA polymerase will move — depends on the meaning within the current context of the sequences that exist at the current locus. Somehow, acting within and guided by its present context, RNA polymerase must have the “good sense” to choose the appropriate activity from among the various possibilities.

And even when the cell would initiate transcription in one particular direction, it must “choose” the exact point in the genetic sequence at which to begin. Different starting points can yield functionally distinct results. “Many studies focusing on single genes have shown that the choice of a specific transcription start site has critical roles during development and cell differentiation, and aberrations in … transcription start site use lead to various diseases including cancer, neuropsychiatric disorders, and developmental disorders” (Klerk and ’t Hoen 2015).

Intertwined with all the preceding issues is the cell’s task of assembling a *pre-initiation complex* (PIC). This variable arrangement of regulatory elements typically sets the stage for the transcriptional activity to follow. Figure 14.2 is a cartoon figure that merely names some of the protein PIC constituents that arrange themselves on DNA (shown as a black line) near locations where gene transcription is to begin. You needn’t concern yourself with names and meanings, beyond the general description I am offering now.

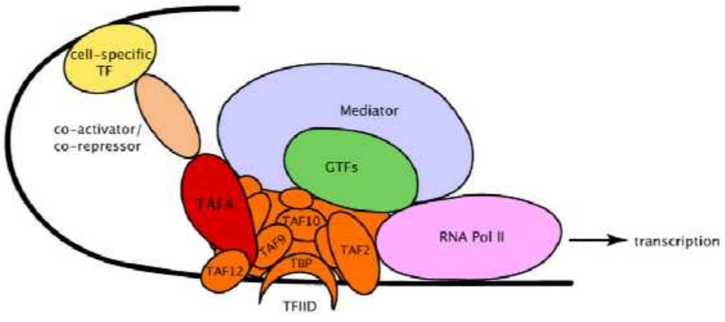

Figure 14.2. The pre-initiation complex (cartoon representation).[7]

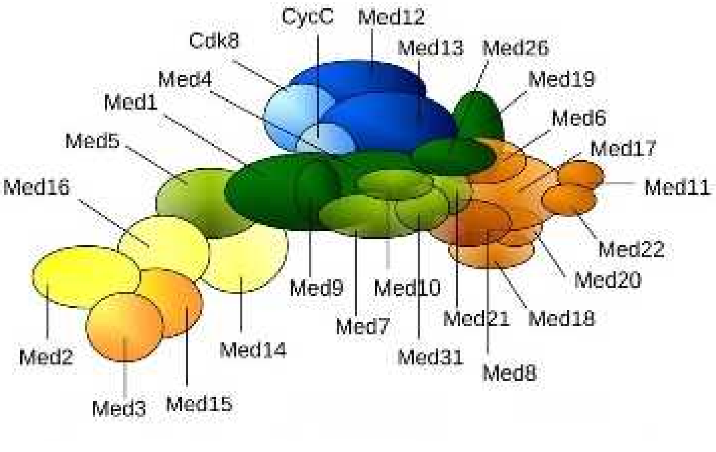

Figure 14.3. Some subunits of the Mediator complex (cartoon representation).[8]

The cell’s narrative at this point could hardly be more dramatic — or more subtle. The largest oval in Figure 14.2, named “Mediator”, is a massive molecule consisting variably of up to 30 protein subunits (Figure 14.3) arranged in modules and interacting in numerous ways among themselves, as well as with other PIC constituents and “visiting” molecules. Depending on context, Mediator can vary endlessly in both subunit composition and function. Its effects upon gene expression are many, and still only fragmentarily grasped.[9]

Figure 14.4 shows the known interaction partners for the Mediator subunits in just one cell type — mouse neural stem cells. The figure omits the numerous interactions among the Mediator subunits themselves. It also omits the interactions among the molecules shown in the surrounding circle. And, perhaps most importantly, it omits the interactions those molecules have with still others not shown in the diagram. For it is just a fact that each of these molecules shown in the outer circle could be made the center of its own diagram. Reflecting on this can usefully remind us of what it means to say that all biological activity in a cell, no matter how micro-focused our vision, turns out upon broader inspection to be an almost impossibly intricate and coordinated activity of the whole.

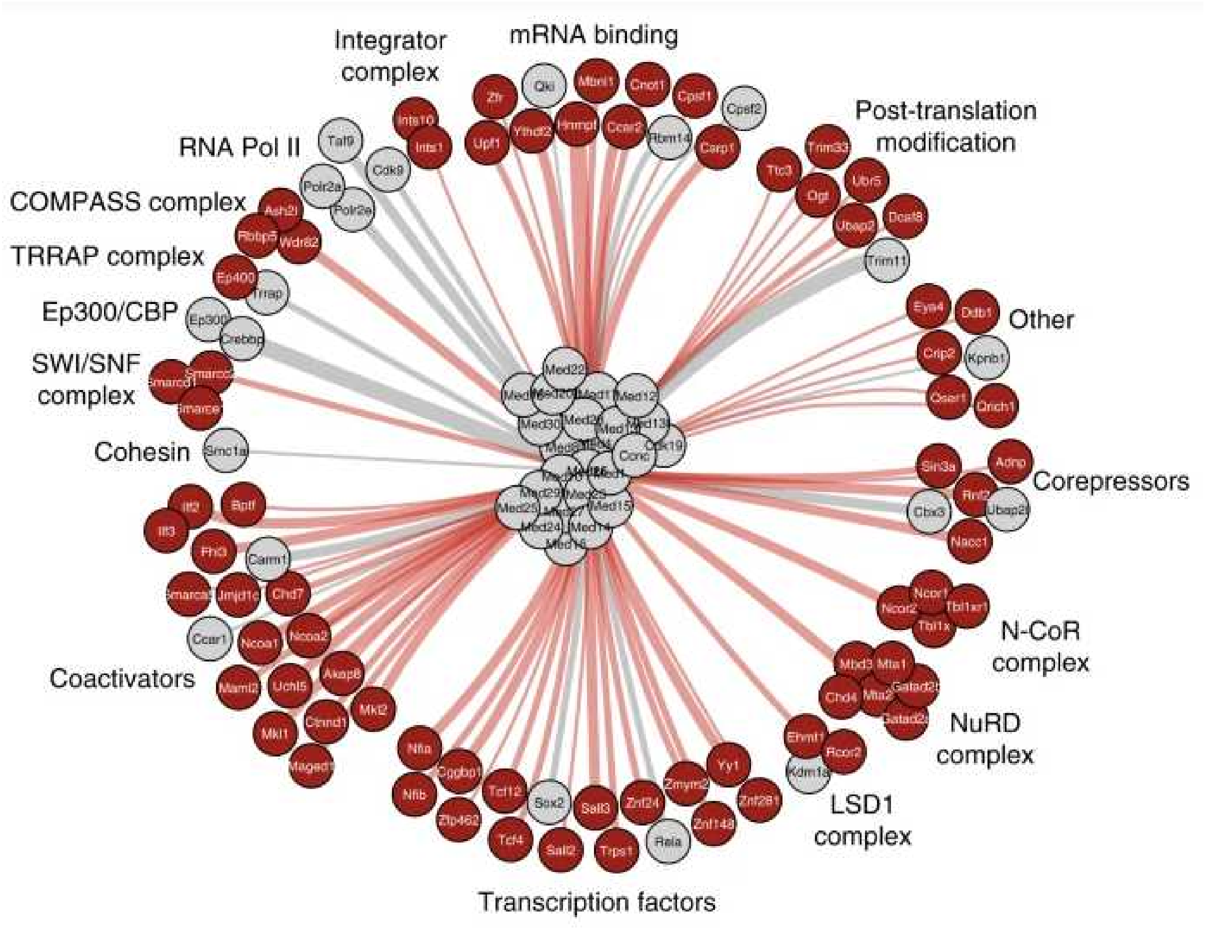

Figure 14.4. Interactions of the Mediator complex in mouse neural stem cells. Mediator subunits are shown in the middle. Gray circles and lines represent interaction partners that were already known at the time (2019) when the research was carried out. Red circles represent interactions newly discovered by the authors of the paper from which this figure was taken.[10]

And, of course, Mediator is just one element of the PIC. Each of the other elements has its own story to tell. The entire PIC was once regarded as a rather mechanical, routine, and mostly unvarying assembly of "parts" whose unproblematic duty was to initiate gene transcription in a standard way. But, of course, that was to overlook how thoroughly every aspect of gene expression *must* vary if it is to serve the needs of a living being. The PIC is now seen to be an infinitely modifiable, highly dynamic complex, responding both to the immediate DNA context and to influences arriving from distant reaches of the cell. Its overall "decision-making" role, which can differ from one gene to the next, is hardly the functioning of a routinely analyzable mechanism.

It doesn't require of the reader a technical penetration of these figures to get a sense for the kind of thing that is going on — especially if one keeps in mind that we are talking, not about rigid machinery of the sort we are familiar with in our daily lives, but rather about *molecular interactions* within a highly fluid context where machine-like constraints to forcibly channel the interactions are altogether absent.

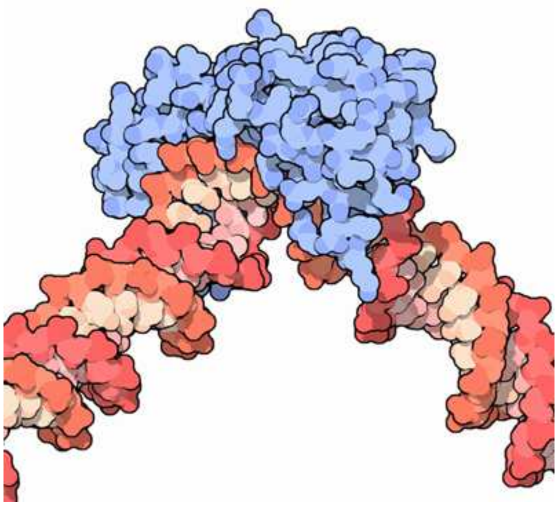

Figure 14.5. DNA (red) in the grip of the tata-binding protein (blue).[11]

I will mention here just one other element of the pre-initiation complex. Figure 14.5 shows DNA (in a wholly artificial, simplistic, and impossibly rigid, concrete representation) being “gripped” by the tata-binding protein (TBP), shown in blue. TBP is also seen as the crescent-moon shape at the bottom of Figure 14.2). The protein “clasps” the DNA in an intimate and rather tortuous manner — a clasp that might remind one of the forcible interaction between two human wrestlers.[12] A severe bend of about eighty degrees is thereby applied to the double helix. This bend, which also tends to pull the two strands of the helix apart, is a general prerequisite for the assembly and activity of the rest of the PIC. As always, the cell is doing something *sculptural*, not narrowly informational in the usual sense.

Carrying on

As we heard at the outset, the (protein) enzyme that transcribes DNA into RNA is *RNA polymerase*.[13] The enzyme certainly does not work alone, however, and its task is by no means automatic. To begin with, its critical interactions with various elements of the pre-initiation complex help determine whether and exactly where transcription will begin. Then, after those “decisions” have been made, RNA polymerase moves along the double helix transcribing the sequence of genetic “letters” into the complementary sequence of an RNA.

Throughout this productive journey, which is called *elongation*, the RNA polymerase still keeps good and necessary company. Certain molecular co-activators modify it during its transit of a gene’s sequence, and these modifications not only enable transcription elongation to begin, but also provide binding sites for yet other proteins that will cooperate throughout the transcription journey. The collective interaction here, as in the activities discussed above, can vary in many details from one context to another — all in order to contribute to a meaningful narrative that could hardly repeat itself in exactly the same way.

The table below offers some perspective on the number and variety of protein factors influencing elongation. You need not puzzle over the details. A quick browse of this incomplete listing (as of 2013) will give you at least an inkling of the kind of intricate complexity the cell must organize in order to carry out transcriptional elongation. As always, it is important to realize that each of the factors listed here enters the picture out of its own world of regulation. At the molecular level of the organism we are always looking at ever-widening circles of interaction, without limit. It’s just a question of how narrowly we choose to focus our attention — and how much of the context we consequently block from view.

Table 14.1. Don’t Read This Table! (Just feel it.) Some factors regulating RNA polymerase elongation (copied from Kwak and Lis 2013).

Class	Factor name	Function	Related factors and notes
GAGA factor	GAF	Generates nucleosome-free region and promoter structure for pausing	NURF
General Transcription Factors	TFIID	Generates promoter structure for pausing	
	TFIIF	Increases elongation rate	Near promoters
	TFIIS	Rescues backtracked RNA polymerase II	RNA polymerase III
Pausing factors	NELF	Stabilizes RNA polymerase II pausing	
	DSIF	Stabilizes RNA polymerase II pausing and facilitates elongation	
Positive elongation factor	P-TEFb	Phosphorylates NELF, DSIF, and RNA polymerase II CTD for pause release	
Processivity factors	Elongin	Increases elongation rate	
	ELL	Increases elongation rate	AFF4
	SEC	Contains P-TEFb and *ELL*	Mediator, PAF
Activator	c-Myc	Directly recruits P-TEFb	
	NF-κB	Directly recruits P-TEFb	
Coactivator	BRD4	Recruits P-TEFb	
	Mediator	Recruits P-TEFb via SEC	
Capping machinery	CE	Facilitates P-TEFb recruitment, counters NELF/DSIF	
	RNMT	Methylates RNA 5’ end to complete capping	Myc
Premature termination factors	DCP2	Decaps nascent RNA for XRN2 digestion	Dcp1a/Edc3

	Microprocessor	Cleaves hairpin structure for XRN2 digestion	Tat, Senx
	XRN2	Torpedoes RNA polymerase II with RNA 5’-3’ exonucleation	
	TTF2	Releases RNA polymerase II from DNA	
Gdown1	GDOWN1	Antitermination and stabilizes paused RNA polymerase II	TFIIF, Mediator
Histone chaperone	FACT	H2A-H2B eviction and chaperone	Tracks with RNA polymerase II
	NAP1	H2A-H2B chaperone	RSC, CHD
	SPT6	H3-H4 chaperone	Tracks with RNA polymerase II
	ASF1	H3-H4 chaperone	H3K56ac
Chromatin remodeler	RSC	SWI/SNF remodeling in gene body	H3K14ac
	CHD1	Maintains gene body nucleosome organization	FACT, DSIF
	NURF	ISWI remodeling at promoter	GAGA factor
Poly(ADP-ribose) polymerase	PARP	Transcription independent nucleosome loss	Tip60
Polymerase-associated factor complex	PAF	Loading dock for elongation factors	SEC, FACT
Histone tail modifiers	MOF	Acetylates H4K16 and recruits Brd4	H3S10ph, 14-3-3
	TIP60	Acetylates H2AK5 and activates PARP	
	Elongator	Acetylates H3 and facilitates nucleosomal elongation	Also in cytoplasm
	Rpd3C (Eaf3)	Deacetylates and inhibits spurious initiation in gene body	H3K36me3
	SET1	Methylates H3K4	MLL/COMPASS
	SET2	Methylates H3K36 and regulates acetylation-deacetylation cycle	Rpd3C
	PIM1	Phosphorylates H3S10 and recruits 14-3-3 and MOF	
	RNF20/40	Monoubiquitinates H2BK123 and facilitates nucleosomal DNA unwrapping	UbcH6, PAF

I will mention here only one aspect of this cooperation of multiple factors. Transcription is an essentially rhythmical performance, with various sorts of pauses along the way. (Again, dynamic sculpture, or dance!) One pause of great significance occurs after RNA polymerase has just begun transcribing DNA but before it has fully separated from the pre-initiation complex. The factors that influence whether transcription will continue at this point — or remain paused for an extended period — play a large role in the regulation of gene expression.

But once that first pause is ended, the elongation journey often continues to be marked by a series of further, generally briefer pauses. These have to do, at least in part, with the need to disengage DNA from its intimate mutual embrace with certain constituents of chromatin (histone complexes, about which we will learn more below). The polymerase has various assistants to aid in this disengagement, which may involve disassembly of the protein complexes. Typical of chromatin in general, these complexes are rich repositories of regulatory information, so they will need to be reassembled behind the transcribing complex, and the remarkably nuanced meanings embodied in their composition and structure will somehow have to be preserved, reestablished, or modified.

So the rhythm of pauses depends, at least in part, on the polymerase's helper molecules and on the positioning of certain protein complexes along the double helix, both of which will vary from one gene to another and even from one time to another. All this, and not just the so-called genetic code as such, shapes the functional significance of the DNA sequence within its chromosomal context. As we will see shortly, different versions of a protein may be produced, depending on the timing of the pauses.

Shaping a significant end

Finally — and mirroring all the possibilities surrounding initiation of gene transcription — there are the issues relating to its termination. Again, they are far too many to mention here. Transcription may conclude at a more or less canonical terminus, or at an alternative terminus, or it may proceed altogether past the gene locus, even to the point of overlapping what, by usual definitions, would be regarded as a separate gene farther "downstream". The cell has great flexibility in determining what, on any given occasion, counts as a gene, or transcriptional unit.

The last part of the transcribed gene is generally non-protein-coding, but nevertheless contains great significance. Examining this region in a single gene, one research team identified "at least 35 discrete regulatory elements" to which other molecules can bind (Kristjánsdóttir, Fogarty and Grimson 2015). Importantly: additional dramatic and diverse regulatory potentials arise from the customized "tail" that the cell commonly adds to the end of an mRNA *after* its transcription from DNA. The regulatory processes called into play by this tail can affect everything from the stability of the mRNA to its cellular localization and the efficiency of its translation into protein. It can even play a role in determining exactly what protein will ultimately be produced. And the patterns of these added tails tend strongly to differ from one tissue type to another. "Decisions" yet again.

Much of this post-transcriptional regulation is accomplished by proteins and other molecules that bind, not only to the end, but also to the various regulatory sequences at the *head* of the RNA transcript. It all occurs in a context-sensitive manner, where cell and tissue type, phase of the cell cycle, developmental stage, location of the transcript within the cell, and converging environmental factors, both intra- and extra-cellular, may all play a role.

But it’s not only the RNA *sequence* that provides opportunities for management by the cell. The three-dimensional, folded *structure* of the molecule offers boundless occasion for further regulation. So here, as with DNA, we find gene expression to be in part a matter of sculptural performance. And, again, it is not just a matter of static form, but of movement. According to molecular biologists at the University of Michigan and Duke University, “RNA dynamics play a fundamental role in many cellular functions”:

> [There are] many structural maneuvers that occur over timescales ranging from picoseconds to seconds … These transitions include large-scale secondary-structural transitions at [greater than tenth-of-a-second] timescales, base pair/tertiary dynamics at microsecond-to-millisecond timescales, stacking dynamics at timescales ranging from nanoseconds to microseconds, and other ‘jittering’ motions at timescales ranging from picoseconds to nanoseconds. RNAs often harness multiple modes to achieve complex "functionality" (Mustoe et al. 2014).

From genetics to epigenetics

“Epigenetics” refers to that which is not genetics as such, but rather is “added to”, or “on top of” genetics. You might therefore think that the transcription factors, RNA polymerases, and other proteins mentioned above, which are not themselves *genetic* elements, would therefore be treated under the heading of epigenetics. Oddly, however, this has not been the case. Presumably, the reason is that these factors have for so long been taken for granted as if they were mere adjuncts to the “controlling logic” of DNA sequences.

But this never made much sense. What I have tried to suggest in my descriptions above is that these “mere tools” are more and more being recognized as participants in a dynamic communal context out of which alone our genes come to disciplined expression according to the needs of each cell.

Now, however, it is time to approach — albeit with painful brevity — what is generally considered the epigenetic mainstream. After all, we now know that gene transcription is merely a small part of all the activity shaping gene expression. The many processes “on top of” transcription are fully as rich and multifaceted as the various features of transcription itself.

We have already heard about *RNA splicing*, which we looked at in Chapter 8, “The Mystery of an Unexpected Coherence”. As we learned in that chapter, cells don’t just passively accept the RNAs that emerge from the transcription process, but rather “snip” them apart and “stitch” (splice) some of the pieces back together, while leaving aside other pieces for purposes both known and unknown. It happens that these operations typically begin before the RNA is fully transcribed, and the rhythm of pauses by RNA polymerase during elongation influences which pieces form the mature transcript.

For the vast majority of human genes the splicing operation can be performed in different ways, yielding distinct protein variants (often called *isoforms*) from a single RNA. It would be hard to find any major aspect of human development, disease etiology, or normal functioning that is not dependent in one way or another on the effectiveness of this liberty the cell takes with the products of its gene sequences.

But RNA splicing is hardly the end of it. Through *RNA editing* the cell can add, delete, or substitute individual "letters" of the RNA sequence.[14] Or, leaving the letters in place, the cell can apply over 170 distinct chemical *modifications* to them.[15] Both the editing and the modifying are major topics in themselves, but not ones we can linger on here.

MicroRNAs: a large world of tiny regulatory factors

An entire, diversified area of research involves small, non-protein-coding RNAs. The only ones we will discuss here are known as *microRNAs* (miRNAs), which are generally derived through the cleaving and processing of longer RNAs. A microRNA commonly joins forces with a large protein complex, called the *RNA-induced silencing complex* (RISC). The microRNA guides the RISC to specific mRNAs by means of (sometimes only rough) base pair complementation. (See "base pair complementarity" in the online glossary at https://bwo.life/mqual/glossary.htm#base_pair.) Once a target mRNA is located, the RISC can cleave or otherwise degrade it, or else block its translation. In this way a typical microRNA can degrade or tune the amounts of a considerable number of different mRNAs.

Such degradation is an example of *RNA decay* in general, for which there are many different, interwoven pathways in cells. It is easy to overlook the fact that decay is fully as important — and fully as much in need of careful regulation — as the production of the RNA in the first place. During development, for example, cell differentiation would be impossible if the RNAs and proteins appropriate for an earlier form of a cell could not be recycled. In this way their constituent nucleotides or amino acids can support synthesis of new RNAs and proteins necessary for the cell's forthcoming, more differentiated form. The same general principle holds for all changing conditions that require fresh responses from the cell.

MicroRNAs are key fine-tuners of the relative numbers of mRNAs in a cell under any given circumstances. We can only wonder how they are "instructed" by the larger context so as to "know" what those relative numbers ought to be. But we do know some of the means employed.

One of the more recent stories about the role of microRNAs in regulating gene expression points to a complexity almost beyond all hope of detailed understanding. Evidence suggests that just about any RNA in the human body can help to regulate any number of other RNAs, just as it in turn is regulated by them. This intertwining of fates is due not only to the competition for resources (an extremely abundant RNA, by monopolizing the available amino acids in a cell, can make it more difficult for other RNAs to be translated into protein), but also to the impact of microRNAs. Here’s how it works:

Many protein-coding RNAs are densely covered with binding sequences for microRNAs, so that a typical microRNA will find about 200 different RNA species it can target for decay or modification. This means that if a particular RNA is being highly expressed — and all the more if it is a “microRNA sponge” possessing multiple binding sites for a specific microRNA — it can have the effect of up-regulating other RNAs that are targets for the same microRNA. It “soaks up” most of the microRNAs that might otherwise degrade those other targets.

The RNAs that in this way regulate other RNAs by competing for shared microRNAs are known as “competing endogenous RNAs” (ceRNAs). Figure 14.6 shows one such interacting network. The ceRNAs are shown in orange boxes, with directly “competing” pairs located at opposite ends of the arrows. The microRNAs mediating the competition are listed alongside the arrows.

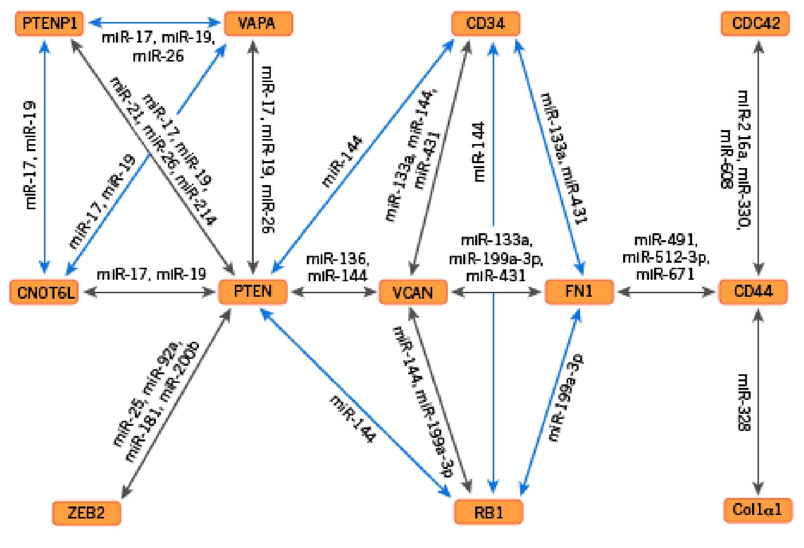

Figure 14.6. Network of competing endogenous RNAs (orange boxes). Gray arrows show where specific microRNAs (miR-25, and so on) are known to bind distinct ceRNAs, and blue arrows indicate possible interactions involving microRNAs known to be present.[16]

Let’s consider just two of the RNAs in the figure. PTEN, when translated, yields a protein that is, among other things, a tumor suppressor. (It also appears to facilitate cell migration, and to play a part in the adhesion of cells to each other.) PTENP1, on the other hand, is an RNA derived from a so-called “pseudogene”, assumed to result evolutionarily from a mutational duplication of the *PTEN* gene, followed by further mutations compromising its protein-coding function. Pseudogenes are one more example of those many DNA elements, once written off as nonfunctional “junk”, which are now being “caught in the act” playing important roles.

In the present case, we know at least one role for PTENP1. Its RNA may be incapable of being translated into protein, but it nevertheless shares many microRNA binding sites with the PTEN RNA. By sequestering those microRNAs away from PTEN, PTENP1 allows the tumor-suppressor to be expressed at proper levels. If, on the other hand, the pseudogene becomes dysregulated for some reason, then microRNAs that would otherwise bind to PTENP1, end up instead binding to, and repressing, PTEN, which reduces its tumor-suppressing activity. It has in fact been shown that PTENP1 functioning is selectively lost in human cancers, consistent with its importance as a microRNA sponge.[17]

And yet, the situation is actually much “worse” than is shown above. MicroRNAs can also regulate other microRNAs, whether by direct targeting or, indirectly, by targeting transcription factors or regulators of those other microRNAs. For example, one particular microRNA (known as miR-499) was shown not only to regulate target genes (via their mRNAs) in the usual way, but also altered the expression of 11 other miRNAs. These changes resulted in 969 down-regulated genes, only 7.8 percent of which were directly targeted by miR-499. In other words, “hundreds of genes may be altered in expression” via these indirect pathways radiating from a single microRNA (Hill and Tran 2021).

Here we see the same obstacle to any straightfoward causal understanding that we encountered above regarding transcription factors activating or repressing other transcription factors. Tracking the mutual, broad-scale, and often subtle interactions where “everything seems to be affecting everything else” will presumably challenge researchers for a very long while. It looks like a classic picture of the unanalyzable holism of all cellular processes. All the other interwoven aspects of gene regulation discussed in this chapter, when added together, only add further to the problem of unanalyzability.[18]

DNA methylation

Some epigenetic processes profoundly implicated in gene expression transform the DNA sequence itself. That is, they modify the nucleotide bases (“letters”) of the so-called “genetic code”. One of these processes is known as *DNA methylation*, which is known to be of extreme importance for gene regulation.

DNA methylation is the addition of a methyl group (with chemical formula $-CH_3$) to certain DNA bases. There are four different bases in DNA, and the one most commonly methylated is cytosine. In its methylated form, this has been referred to as the “fifth base of DNA”. Millions of bases throughout the genome are selectively and dynamically methylated in the cells of normal human tissues. The difference between a methylated and unmethylated base is hardly less significant, in its own way, than the difference between one base and another. But, unlike the general rule for the “raw” sequence of DNA bases, the methylation of those bases can be altered during development and in response to environmental influences. In this sense, much of our DNA inheritance is not at all the fixed-once-and-for-all destiny it is so often taken to be. (And, of course, just about everything else discussed in this chapter makes the same point.)

An “attached” methyl group is said to “tag” or "mark" the affected base. However, words such as “attach”, “tag”, and “mark” are grossly inadequate, suggesting little more than an annotation in the margin of a text, or a digital label on an otherwise unchanged entity. But in fact what DNA methylation gives us is chemical transformation — the metamorphosis of many millions of letters of the human genome under the influence of pervasive and incompletely understood cellular processes. And the altered balance of forces — the modulation of chemical, electrical, and sculptural qualities of chromosomes — resulting from all these chemically transformed bases, certainly plays with endless possible nuances into the expression of our genes.

We have been learning about the extreme consequences of these metamorphoses. In the first place, the transformations of structure brought about by methylation can render DNA locations no longer accessible to the protein transcription factors that might otherwise bind to them in order to activate nearby genes. On the other hand, by changing the local physical properties of the double helix, methylation "is observed to either inhibit or facilitate [DNA] strand separation, depending on methylation level and sequence context" (Severin et al. 2011). This has a direct effect on gene expression — for example, because strand separation is essential for the work of the polymerase that transcribes DNA.

Many proteins that recognize and bind specifically to methylated sites are then able to recruit other proteins that restructure and functionally alter the chromatin — for example, condensing it in a manner conducing to gene repression throughout an entire chromosomal region.

It would be difficult to overstate the pervasive role of this epigenetic factor in the organism. Stephen Baylin, a geneticist at Johns Hopkins School of Medicine, says that the silencing, via DNA methylation, of tumor suppressor genes is "probably playing a fundamental role in the onset and progression of cancer. Every cancer that's been examined so far, that I'm aware of, has this [pattern of] methylation" (quoted in Brown 2008). In one study among various others — a study of colorectal cancer tissues — the researchers identified 1549 genomic regions with methylation patterns differing from the patterns in similar, non-cancerous tissues (Wei et al. 2016). There are often many more methylation anomalies in cancerous tissues than there are mutated genes.

In an altogether different vein, researchers have found that "DNA methylation is dynamically regulated in the adult human nervous system". Distinctive patterns of DNA methylation are associated with Rett syndrome (a form of autism) and various kinds of mental retardation. Changing patterns of methylation also figure in aging, and constitute a "crucial step" in memory formation (Miller and Sweatt 2007).

Among many other things, DNA methylation appears to play a key role in tissue differentiation; in the activation (rather than only the repression) of gene transcription; and in the regulation of alternative RNA splicing. And, as by now we might expect, DNA methylation itself is regulated by processes converging from all corners of the cell and larger context.

The nucleosome: a complex marriage of DNA and protein

Nothing more vividly illustrates the cell's dynamic and transformational "embrace" of its DNA than the thirty million or so *nucleosomes* that form the main bulk of human chromosomes. Each nucleosome consists of several histone proteins complexed together in a *core particle*, around which various other proteins help to bend and wrap the rather stiff DNA double helix. The DNA circles the core particle approximately twice and is (more or less) held in place there, largely by means of electrostatic forces and hydrogen bonding. It is time to focus on this remarkable protein-DNA complex — a complex that, for all its centrality, scarcely figures in the broader public understanding of genetics.

Figure 14.7 is an electron microscope-derived image published in the journal *Science* in 1974, the decade when the nucleosome's existence was discovered by a team of researchers at the University of Tennessee and Oak Ridge National Laboratory. You can see the nucleosomes as "beads" along the string-like DNA.

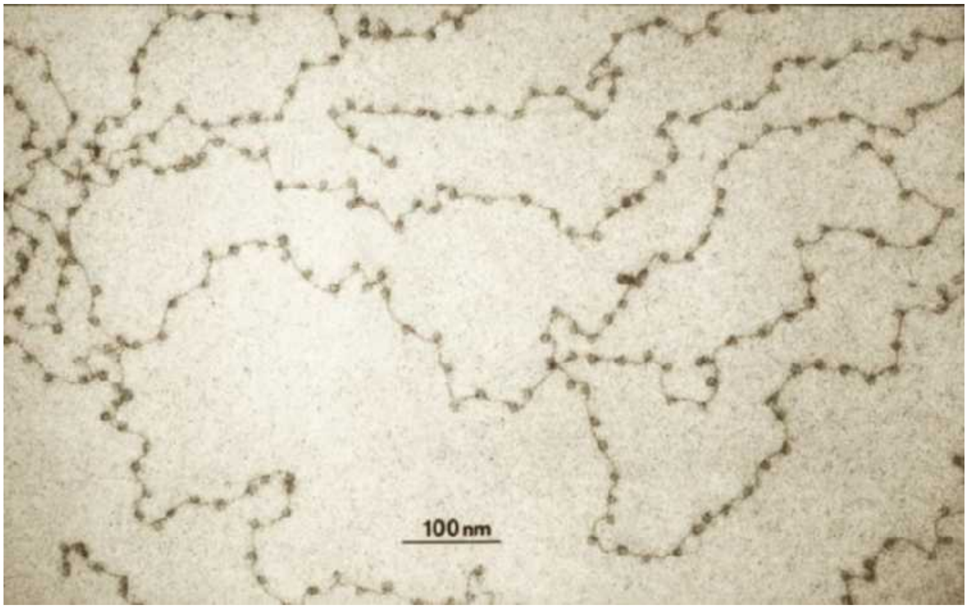

Figure 14.7. DNA (black "string") and nucleosomes ("beads" on the string), as imaged by an electron microscope.[19]

A nucleosome most commonly consists of eight histone proteins (two copies of each of four histones, known as H2A, H2B, H3, and H4). The two stretches of *linker DNA* at the entry and exit points of the nucleosome, are typically held together by a *linker histone* (H1). The latter plays a role, both in influencing how the DNA is bound to the core particle, and also in managing the packing together of neighboring nucleosomes.[20] (See the cartoon representation in Figure 14.8.)

I referred earlier to the challenge of packing all the DNA of a cell into the space of the nucleus. As it happens, nucleosomes play a large role in this packing. Depending on their arrangement, which varies with the context, they help to organize the DNA molecule into a fiber that is said to be anywhere from (roughly) 1/5 to 1/50 of the uncondensed length. Something like 75 percent of our genome is wrapped up in nucleosomes, and a typical gene will have scores of nucleosomes within its body. This radically alters the popular image of a chromosome as a vast, uninterrupted length of the spiraling double helix.

Figure 14.9 shows (again in cartoon form) nucleosomes with and without linker histones, as well as the varying degrees of DNA compaction that can be achieved with the aid of nucleosomes.

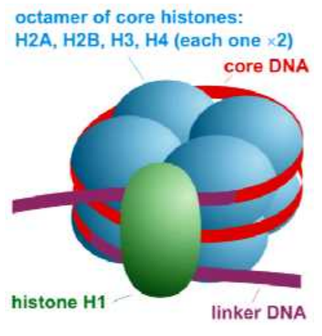

Figure 14.8. A schematic representation of a nucleosome, together with the linker histone (H1) and the encircling DNA.[21]

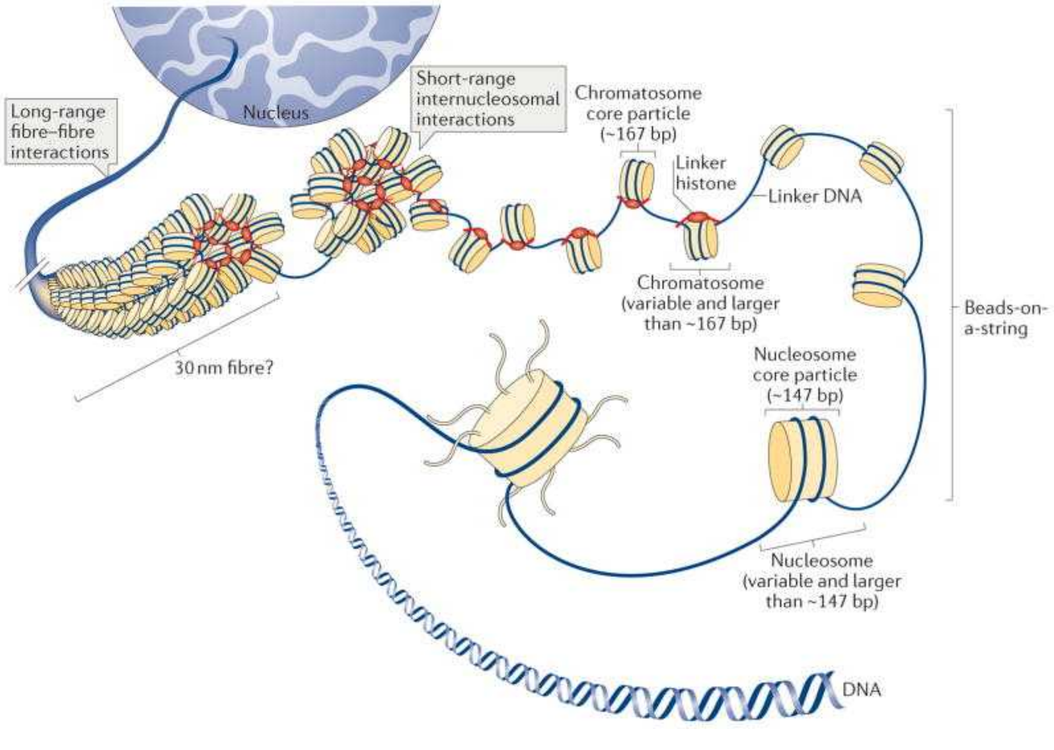

Figure 14.9. Levels of chromatin folding and compaction. Here the “chromatosome core particle” refers to the nucleosome core particle with linker H1 added. (However, all such histone-plus-DNA configurations can still be referred to as “nucleosomes”.) The abbreviation “bp” refers to nucleotide base pairs, so that “167 bp” and “147 bp” refer to the approximate length of DNA wrapped around nucleosomes with and without linker histones, respectively. DNA is ever more fully compacted as the nucleosomes are packed more tightly together. For simplicity, DNA-bound proteins other than histones are not shown. Also, only histone-DNA interactions on a single chromatin fiber (chromosome) are depicted here, not interactions among different chromosomes.[22]

"Ribbon" images of the nucleosome core particle, as in Figure 14.10, though highly schematic, are intended to signify certain abstract features of the histone protein structure. The DNA encircling the histones is shown, cartoon-like, in purple.

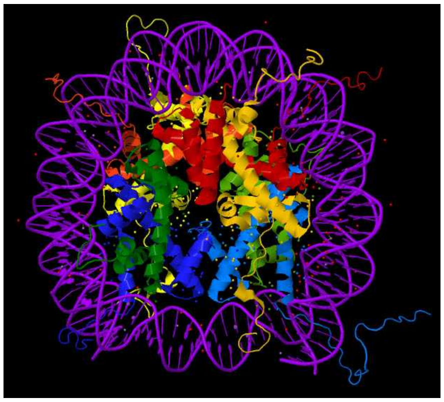

Figure 14.10. A "ribbon" representation of nucleosome structure.[23]

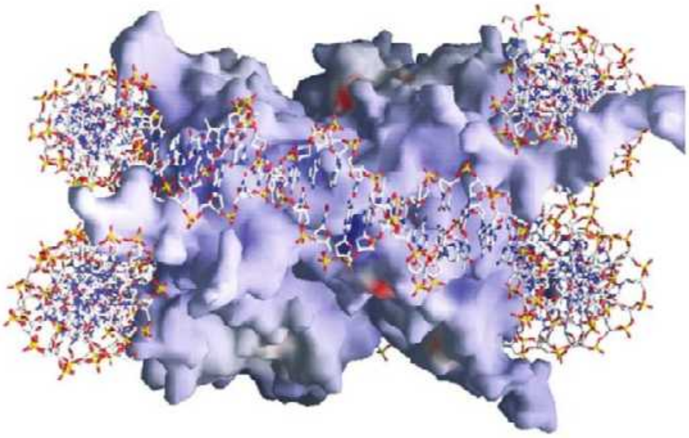

Figure 14.11. Yet a different way to represent the structure of a nucleosome. See main text.[24]

And yet again, though still with extreme artificiality in terms of the visual image, we have representations such as Figure 14.11, which are generated using data from sophisticated molecular imaging techniques. The red, white, and blue stick figure represents the DNA encircling (about one and two-thirds times) the histone core particle. Red and blue patches on the core particle represent acidic and basic areas, respectively. These, via their effect on the distribution of electrostatic charge over the surface of the histones, have a bearing on many of the functional aspects of the nucleosome discussed below.

Here it is well to remember one of the primary lessons of twentieth-century physics: we are led disastrously astray when we try to imagine atomic- and molecular-level entities as if they were tiny bits of the stuff of our common experience. It would be far better to think of the core particle's "substance", "surface", "contact points", and "physical interactions" as forms assumed by mutually interpenetrating forces in their intricate and infinitely varied play.

In particular, as geneticist Bryan Turner of the School of Cancer Sciences at the University of Birmingham (UK) reminds us, the nucleosomal core particle "is much more flexible than the crystal structure [which is the basis for images like Figure 14.11] might lead us to believe", and our current understanding of it "does not lend itself to simplifying generalisations" (Turner 2014). As we will see, the impressive enactments of form and force about the nucleosome are central to any understanding of gene function.

Every "thing" in biology is really an activity, or is caught up in activity, and the extraordinarily dynamic nucleosome is no exception. For example, nucleosomes are the primary feature of chromatin that, as we noted earlier, must be disassembled, or at least "remodeled", during gene transcription, and then restored to a fully functional state after the transcribing enzyme (RNA polymerase) has passed by.

More generally, the individual histones in a nucleosome can come and go at an almost alarming rate — with an average exchange time of just a few minutes for many nucleosomes. And in some situations the histones exchanged in this way can be *different* histones — known as “histone variants” — with each variant exerting its own distinct sort of influence on gene expression and chromatin dynamics. Individual histones can even be removed from a core particle altogether, leaving it “incomplete” and now with seriously altered function.

Further: in the course of its life the cell can, and does, reposition huge numbers of nucleosomes along the double helix, bringing to bear upon them a whole galaxy of regulatory interactions. The positioning of nucleosomes — which may be achieved by protein complexes that slide the DNA around the core particle — matters at a highly refined level: a shift by as little as two or three bases (two or three “letters” of the “genetic code”) can make the difference between an expressed or silenced gene (Martinez-Campa et al. 2004). (Individual genes typically contain thousands of bases.)

Still further: not only the exact position of a nucleosome along the double helix, but also the precise *rotation* of the helix in its embrace of the histones is important. “Rotation” refers to which part of the DNA double helix faces toward a histone surface and which part faces outward. Depending on orientation, the nucleotide bases will be more or less accessible to the various gene-activating and repressing factors that recognize and bind to specific sequences.

This in turn relates to the fact that there are two grooves (the *major* and *minor* grooves) running the length of the double helix (Figure 14.12). Proteins that recognize a particular sequence of nucleotide bases typically do so in the major groove, where the sequence is most readily accessible.

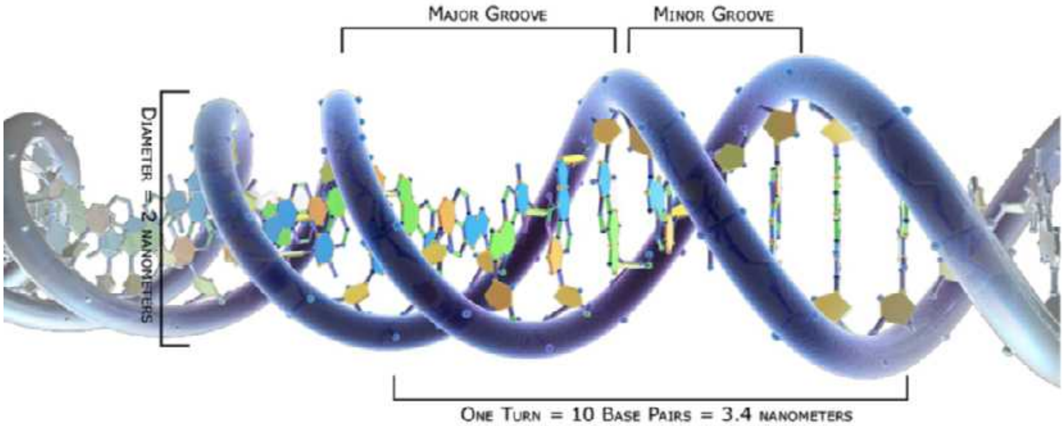

Figure 14.12. A schematic representation of the DNA double helix, showing the major and minor grooves.[25]

However, many proteins bind to DNA in highly selective ways that can be determined by factors other than the exact DNA sequence. For example, investigations have shown that the minor groove may be compressed so as to enhance the local negative electrostatic potential. Regulatory proteins “read” the compression and the electrostatic potential as cues for binding to the DNA. The “complex minor-groove landscape” (Rohs et al. 2009) is indeed affected by the DNA sequence, but also by associated proteins. Regulatory factors “reading” the landscape can hardly do so according to a strict digital code. By our musical analogy: it’s less a matter of identifying a precise series of notes than of recognizing a melodic and harmonic motif performed by a full orchestra.

You can see, then, why one molecular biologist has referred to the “bewildering array of molecular mechanisms that have evolved to alter the physical properties of nucleosomes” and thereby to play a role in gene regulation (Cosgrove 2012). Also consider this:

> Influences such as DNA methylation, posttranslational modifications of the core histone proteins, histone variants, [histone gene] mutations and the level of chromatin compaction may each contribute to a multitude of additional energy states within the chromatin network. All these factors can potentially alter intra- and internucleosomal forces and establish a different or more extended ensemble of nucleosome conformational states, and therefore further fine-tune the functional activities. This is consistent with the notion of a heterogeneous population of nucleosomes within chromatin, all in a dynamic state and able to respond to continuous changes from environmental ques [sic] (Joshi et al. 2012).

But our story of nucleosome-based regulation has so far been radically incomplete.

A tale of tails

We will now look more closely at those parts of the nucleosome where it may be that the most dramatic story unfolds. Below is an enlarged view of Figure 14.10, representing a nucleosome. The eight histones of the core particle are shown as a ribbon diagram, with the DNA double helix (schematically depicted in purple) wrapped around it somewhat less than two times. You will note a number of squiggly “pig’s tails” extending outward from the core histones. These are the thin, flexible, and mobile *histone tails*, ten of which are present in the typical core particle. There are hundreds of distinct chemical modifications of these tails (referred to as *post-translational modifications*), and the countless resulting patterns of modification within any given nucleosome or group of nucleosomes are intimately bound up with the expression of genes. In fact, there is little relating to gene regulation, DNA replication, chromatin structure and dynamics, or the overall functional organization of the nucleus that is not correlated in one way or another with patterns of histone tail modifications.

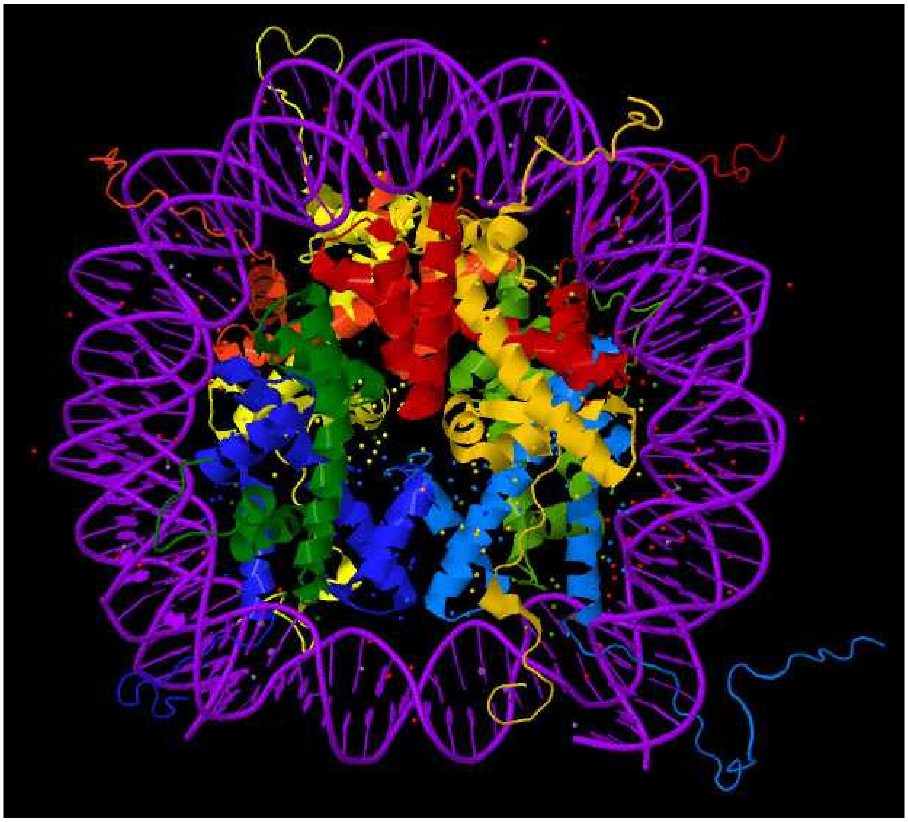

Figure 14.13. Enlarged view of Figure 14.10.

Learning about these tails, we may be reminded (albeit in a highly fanciful manner) of both the sensory functions of insect antennae and the motor functions of limbs. On the "sensory" side, the tails are receivers of molecular signals coming from all directions in the form of post-translational modifications. The nucleosome provides a context where the integrated significance of these signals can be "read off" (to use the standard phrase) by the gene-regulatory proteins that are sensitive to them. These readers may then "recruit" (again standard usage) various other proteins that either help to restructure chromatin in one way or another, or more directly regulate the expression of genes.

There are in fact many protein "readers" that interact with single modifications, or with groups of them, or with the asymmetrically modified tails of a histone pair, or with a histone modification in proximity to a site of DNA methylation. Every such reader protein acts out of its own world of biochemical genesis, folding, post-translational modification, and conformational plasticity, and together these proteins tell an important part of the story of gene regulation.

Finally, the tails can also act with a kind of brute force as "muscular" effectors. They can, for example — no doubt depending at least in part on their various modifications and protein associations — insinuate themselves into one of the grooves of the double helix, thereby loosening the DNA from the nucleosomal core particle (and making it more available for transcription), or else binding it more tightly. In both cases, one way this is accomplished is by altering the electrical balance between histone and DNA.

Some of those tails are also thought to establish nucleosome-to-nucleosome contacts, helping to compact a stretch of chromatin. How and whether this is done can make genes either more or less accessible for transcription and various forms of regulation.

Perhaps you can now see why the members of one research team, writing about histone tail modifications, find themselves reflecting upon

> the incredibly intricate nature of the chromatin landscape and resultant interactions. The biological consequences of [interactions between histone tail modifications and regulatory proteins] are highly context dependent, relying on the combinatorial readout of the spatially and temporally fluctuating local epigenetic environment and leading to a highly fine-tuned [regulation] of particular genomic sites (Musselman et al. 2012).

A still closer look

We have progressively magnified our field of view by shifting from the overall structure of chromatin, to the nucleosome with its histone core, and then to the individual histone tails. Important principles of gene regulation operate at each different level. Now, magnifying our view one last time, we will home in on a single histone tail modification. The most commonly discussed modifications are the *acetylation* and *methylation* of certain lysine amino acids in the tails, but there are many other kinds of modification. Here I will focus on the modification called *ubiquitination* simply because its gene regulatory roles do not seem quite as extensive (or just are not as well investigated) as those performed by some other tail modifications. This makes their description here a little more manageable.

Monoubiquitination is the “attachment” (a poor word, as I indicated above) of a single ubiquitin chemical group to a lysine amino acid of a protein. In the case of histone tails, this can be done at more than one lysine, but we will look only at the monoubiquitination of lysine 120 on the tail of the histone known as H2B, all of which can be designated *H2BK120ub1* (where ‘K’ is the symbol for lysine), but which will be abbreviated here as H2Bub1.

So what is the significance of this modification at a single histone tail location? Here’s one summary:

> H2Bub1 takes part in almost every molecular process associated with chromatin biology. H2Bub1 has been shown to regulate transcription initiation and elongation, DNA damage response and repair, DNA replication, nucleosome positioning, RNA processing and export [from the nucleus], chromatin segregation and maintenance of chromatin boundaries. Given the large number of molecular processes regulated by H2Bub1, it is not surprising that H2Bub1 plays a vital role in some of the most fundamental biological processes that occur within multicellular organisms. [Loss of an enzyme responsible for ubiquitination] results in very early embryonic lethality. Furthermore, aberrant H2Bub1 levels can affect cell cycle progression, apoptosis [“programmed cell death”], stem cell differentiation, development, viral infection outcome and "tumorigenesis" (Fuchs and Oren 2014).

(I draw largely on the paper by these authors in the remainder of this section.)

Of course, H2Bub1 does nothing “in general”; results are always specific and context-dependent. For example, blocking this modification in a particular human cell line was found to upregulate some genes, downregulate others, and leave a great many unchanged. Under some circumstances, H2Bub1 is particularly needed for the transcription of relatively long genes. And the modification also plays an important role in histone "crosstalk", helping to regulate other crucial modifications within the same or on different histones.

A search for "effector" molecules that, singly or cooperatively, associate and interact with the H2Bub1 modification led to the identification of more than ninety proteins, many with known functions in gene regulation consistent with those known to be "effects" of H2Bub1. This points us to what could be a still further extension of our survey, whereby we might analyze one or more of those proteins. We would then have to trace the modifications *they* undergo, and the larger regulatory world in which they are caught up. But there would be no end of this, since following up any particular line of inquiry in a cell or organism sooner or later leads to everything else.

I have made repeated reference to these ever-widening circles of causal influence. Here I will just momentarily hint at this broader reality in relation to the histone tail modifications called "methylation" (not to be confused with DNA methylation). A methyl group is added to various histone amino acids by enzymes called "methyltransferases", and is removed by other enzymes called "demethylases". The mammalian genome is said to encode thirty five histone methyltransferases and twenty three demethylases. This is where the complications enter.

In an article entitled "Controlling the Controllers", the authors discuss how these methylating and demethylating enzymes are themselves modified and regulated by the addition of phosphoryl groups, with "diverse effect" on enzyme function. Further, the phosphorylation of the enzymes is in turn "regulated by upstream signalling pathways". And, still further, "different histone methyltransferase and demethylase enzyme families are connected to upstream signalling pathways in different ways" (Separovich 2020). And so the circles widen. But now we must return to our narrower focus.

It remains to mention only that, with ubiquitination as with so many other molecular biological investigations, researchers are vexed by an imagined "need to establish causality more unequivocally" (Fuchs and Oren 2014) — a need that never seems fully satisfied as our understanding grows. This search for unambiguous causes is a fruitless one (Chapter 9), because the kinds of causes being looked for don't exist in organisms.

As for the relations that do exist in organisms, just reflect for a moment. Think, for example, of the transcription network depicted in Figure 14.1. Then think of the networks of hundreds of mutually regulating mRNAs and microRNAs also discussed above and illustrated in Figure 14.6. And now consider the virtually infinite combinations of histone tail modifications and their endlessly elaborated meanings and pervasive "crosstalk". Many other domains of gene regulation have been alluded to in preceding sections, and untold others *could* have been mentioned. And now ask yourself what all this must mean. There seem only two possibilities: complete bedlam and chaos of causes working at cross-purposes, or else the play of an encompassing wisdom whose all-embracing effectiveness and power of coordination we can hardly yet even begin to conceive.

Movement and rhythm

Few if any details of nucleosome structure and dynamics are fixed and constant. Nothing illustrates this more vividly than the fact of *DNA breathing* on the nucleosome surface. This refers to the partial and rhythmical unwrapping and re-wrapping of the double helix, especially near the points of entry and exit on the nucleosome. This provides what are presumably well-gauged, fractional-second opportunities for gene-regulating proteins to bind to their target DNA sequences during the periods of relaxation:

> Some transcription factors (TFs) only recognize nucleosomal DNA when nucleosome "breathing" occurs, that is when the DNA is partially and temporarily unwrapped from the nucleosome surface … histone post-translational modifications facilitate DNA breathing. TF binding facilitates further nucleosome unwrapping by promoting the binding of additional TFs, and/or in coordination with chromatin remodelers. Some TFs can bind their cognate motifs on fully compacted nucleosomal DNA and initiate ATP-independent DNA unwrapping or even histone eviction. However, outcomes in which TF binding stabilizes nucleosomes are also possible (Makowski, Gaullier and Luger 2020).

This breathing also relates to the transcriptional pausing by RNA polymerase (discussed above). The polymerase appears able to take advantage of the breathing in order to move, step by step and with significant pauses, along the genes it is transcribing. In this way the characteristics of nucleosomes — how the DNA breathes, and whether it is firmly or loosely anchored to the histones — can affect the timing and frequency of pauses. And, as we saw earlier, the rhythm of pauses and movements then affects the splicing and folding of the RNA being synthesized, which in turn bear on how the RNA can be regulated as well as the structure and function of the protein molecule produced from the RNA. A proper "music" is required for the overall performance to be successful. So it appears that the references to "choreography" and "dance" one sometimes encounters in the literature may be more than mere poetic niceties.

With a different sort of rhythm nucleosomes will sometimes move — or be moved (as I have remarked before, the distinction between "actor" and "acted upon" is forever obscured in the living cell) — rhythmically back and forth along the DNA, shifting between alternative positions in order to enable multiple transcriptional passes over a gene by RNA polymerase.

Stem cells exhibit what some have called "histone modification pulsing", which results in the continual application and removal of both gene-repressive and gene-activating modifications of nucleosomes. In this way a delicate balance is maintained around genes involved in development and cell differentiation. The genes are kept, so to speak, in a finely poised state of "dynamic and balanced readiness", so that when the decision to specialize is finally taken, the repressive modifications can be quickly lifted, leading to rapid gene expression (Gan et al. 2007).

This state of suspended readiness in stem cells also seems to be served by a rhythmical (10 – 100 cycles per second), back-and-forth spatial movement, or vibration, of chromatin within the cell nucleus. Associated with “hyperdynamic binding of structural proteins” mediated by nucleosomes, this vibration is thought to help maintain the largely open chromatin state characteristic of stem cells. The movement depends on the metabolic state of the cell and is progressively dampened as the stem cell differentiates into a specialized cell with substantial portions of its chromatin in a condensed state (Hinde 2012).

But quite apart from stem cells, it is increasingly appreciated that nucleosomes play a key role in holding a balance between the active and repressed states of genes in many cell types. As the focus of a highly dynamic conversation involving histone variants, histone tail modifications, and innumerable chromatin-associating proteins, decisively placed nucleosomes can (as biologist Bradley Cairns writes) maintain genes “poised in the repressed state”, and “it is the precise nature of the poised state that sets the requirements for the transition to the active state”. Among other aspects of the dynamism, there is continual turnover of the nucleosomes themselves — and of their separate components — a turnover that allows transcription factors to gain access to DNA sequences “at a tuned rate” (Cairns 2009).

It is perhaps worth mentioning here that in certain bacteria a 24-hour (circadian) rhythm correlates with the changing state of DNA supercoiling — that is, with a tighter or looser twisting of the double helix. It appears that something similar may be going on in higher animals, where DNA supercoiling is so closely “wrapped up” with nucleosomes. In these organisms one of the factors involved in the extremely complex processes by which genes are regulated in a circadian fashion is the rhythmic application of histone modifications to selected nucleosomes (Woelfle et al. 2007), presumably with direct implications for chromatin structure and DNA supercoiling.

The nucleosome, we can fairly say, is a ceaselessly transforming matrix and organizational hub whose

Box 14.1

From Static Mechanism to Dynamic Regulator

In an article entitled “Understanding Nucleosome Dynamics and Their Links to Gene Expression and DNA Replication”, Pennsylvania State University molecular biologists William Lai and Franklin Pugh concluded their review of nucleosomes this way:

“Originally viewed as a rather static mechanism of chromatin packaging, the nucleosome core complex is now well recognized as one of the key regulatory components of the genome. We also now see that instead of static protein complexes, nucleosomes are in fact exceptionally dynamic and that their positioning and composition are crucial for genome regulation. As such, the study of nucleosome dynamics is essentially the study of genome regulation. The complex interaction between nucleosome occupancy and positioning allows the cell to properly regulate accessibility of various proteins and their complexes to DNA and thus to regulate gene expression programmes. A variety of regulatory cofactors such as chromatin remodellers, chaperones and general regulatory factors operates both independently and synergistically to maintain the precise organization and composition of nucleosome arrays at specific genomic loci. This dynamic environment probably exists so that the genome may respond and adapt quickly to both external stimuli as well as be able to quickly recover from chromatin-disruptive activities such as transcription and replication” (Lai 2017).

With reference to that last sentence, it needs adding that what “responds and adapts quickly” to external and internal stimuli is not really the rather passive genome so much as the entire, all-encompassing regulatory environment, of which the nucleosome is a neat picture and summary.

structure and pattern of activity is never exactly duplicated anywhere in the genome. It is where the infinitely ramified interface between the larger cell and its DNA comes to its most focal expression. And that expression turns out to be livingly nuanced activity, dynamic beyond what anyone imagined during the age of the double helix as the one-dimensional “secret of life”.

And so, seemingly in the grip of the encircling DNA with its relatively fixed and stable structure, yet responsive to the ceaselessly varying flows of life around it, the nucleosome holds a muscular and intelligent balance between gene and context — a task requiring flexibility and a play of appropriate rhythm.

Such, then, is the intimate, intricate, well-timed choreography through which our genes come to their proper expression. And the plastic, shape-shifting nucleosome in the middle of it all provides an excellent vantage point from which to view the overall drama of form and movement.

A story mostly untold

We have, in our review, only sparsely sampled the overwhelming number of causal factors participating in gene expression. The topics not touched upon here — the unmentioned domains of regulatory, or epigenetic, activity affecting what the cell makes of its genes — would extend the presentation vastly beyond what I have briefly alluded to here.

There is, for example, the recently intensifying exploration of the importance of modifications, not only on the histone tails, but also on the histone cores. These also are proving relevant to gene expression, and in complex ways, both direct and roundabout.

We could also have talked about the entire universe of regulation governing the translation of mRNA molecules into protein after they have been exported from the cell nucleus into the cytoplasm. The task is accomplished by complexes of protein and RNA known as “ribosomes”. The diverse factors the cell gathers together for translation rival those we see in gene transcription.

And once a protein is generated, there is the problem of its folding (and re-folding), often with the help of “chaperone” proteins. Many proteins can potentially fold in an almost unlimited number of ways, yet achieving the “right” folds is crucial for protein function. We have seen that both alternative splicing and folding of an RNA can occur (with major functional implications) during its *transcription* from DNA. Similarly, the folding of a protein can begin during its *translation* from RNA. Moreover, the folding outcome may be affected by the innumerable factors playing into the activity of translation. We do not often find just one thing at a time being accomplished by any biological process.

Then, still further downstream from gene transcription, there are the various post-translational modifications (PTMs) that may be applied, removed, and re-applied to any gene-regulatory protein (transcription factors, co-activators, co-repressors, chromatin remodelers, and so on), just as we saw with the histone proteins belonging to nucleosomes. These again shape the molecule’s function, often in a dynamic, ever-shifting way as the modifications come and go. Together, the many thousands of proteins subject to PTMs, and the diverse effects of these modifications, make for a vast regulatory landscape almost impossible to comprehend. The resulting regulatory activity is always context-dependent, relating to larger, governing purposes rather than being the mere effect of a local physical necessity.

We could also talk about what is, in one sense, the most fundamental biological activity of all — metabolism. After all, every performance of our body derives in one way or another from the food we eat. Metabolites and the organization of metabolic processes play critical roles in many aspects of gene expression related to everything from circadian rhythms to cancer.

Or we could talk about how some RNAs, especially non-protein-coding RNAs, form a "scaffolding" that gives structure to the cell nucleus and therefore plays a fundamental role in just about all nuclear functions. Except that words such as "scaffolding" and "structure" can be very misleading, as two researchers point out in a paper entitled "Role of Nuclear RNA in Regulating Chromatin Structure and Transcription". We should expect, they write, that "any nuclear structure that is assembled employing RNA cannot be static but [must be] constantly recycling degraded RNA with newly synthesised ones". So "the original concept of a static nuclear matrix must be re-evaluated in terms of a dynamic scaffold" (Michieletto and Gilbert 2019).

Perhaps the most intense and significant new field of research bearing on gene regulation in recent years relates to *phase transitions* in the cell, and especially in the nucleus. Like ice crystals forming and dissolving in water held near the freezing point, or like oil droplets in some other liquid (or like water droplets in oil), complex combinations of proteins, RNAs, and other molecules can form separated-out liquid or semi-solid aggregates within the cellular plasm. The dynamic functional role of these aggregates in bringing molecular communities together at the right place, in the right amounts, and at the right time is now a prime topic relating to just about everything discussed in this chapter. The new understanding we are gaining in this field makes a mechanistic or deterministic interpretation of cellular physiology even less tenable than it already was.

And if any new field of research ranks second to phase transitions in importance, it surely must be the one focusing on the role of the *microbiome*. The collective DNA sequences of the microorganisms in our bodies exceeds that of the trillions of human sequences in all our cells collectively. The processess rooted in this "foreign" DNA can affect our biology, much as can the processes stemming from our own DNA. And the effects extend to regulation of our genes.

But surely it is time for us to stop. Anyone desiring a glimpse of the wider range of topics relating to gene expression might wish to scan the expanded outline of topics near the beginning of the article, "How the Organism Decides What to Make of Its Genes (Talbott 2021).

Concluding thoughts

A decisive problem for the classical view of DNA is that a human cell employs its 21,000 or so genes to generate an estimated 250,000 to 1 million distinct proteins (Klerk and ’t Hoen 2015). The activities shaping these abundant outcomes are not strictly determined by DNA. Rather, they arise from all corners of the cell and larger organism, just as the outcomes themselves — all those distinct proteins — are ushered to their proper places in every tiniest niche throughout the whole. We are always watching integral and unified performances. The idea that genes are *originating* causes that make everything else happen is grotesquely wrong-headed.

Mina Bissell, a researcher who has received many recognitions, has put the matter this way: “The sequence of our genes are [sic] like the keys on the piano; it is the context that makes the music” (Bissell and Hines 2011). We might add that the raw DNA sequence does not even contain all the keys; let’s say: just the white keys. The flats and sharps, without which the music would lose its savor, are provided by DNA methylation, RNA editing, and so much more.

And Shelley Berger, the Daniel S. Och professor of cell and developmental biology at the University of Pennsylvania School of Medicine’s Wistar Institute — after noting that a single histone tail modification “recruits numerous proteins whose regulatory functions are not only activating but also repressing”, and that “many of these marks have several, seemingly conflicting roles” — summarized the situation this way:

> Although [histone] modifications were initially thought to be a simple code, a more likely model is of a sophisticated, nuanced chromatin “language” in which different combinations of basic building blocks yield dynamic functional outcomes (Berger 2007).

What she says about histone tail modifications could just as well be said, as we have seen, about the entire universe of gene regulation. We are looking at a meaningful, qualitative, and thoughtful language through which living narratives are constructed. In slightly different terms, Berger envisions histone modifications as participating in “an intricate ‘dance’ of associations”.

In the plastic organism, what goes on at the local level is always shaped and guided by a larger, coherent context — a context that surely has meaning, but (as in natural languages) never an absolutely fixed grammar or logic. And, in fact, while overwhelming evidence for a meaningful, gene-regulatory conversation involving histone modifications has emerged, there is little to suggest a rigid code — this despite the strong urge in molecular biologists to find one.

The overall picture of gene expression is one of unsurveyable complexity in the service of remarkably effective living processes. What all the foregoing shows is that the whole cell and the whole organism are forever carrying out *narrative* tasks. We have no explanatory coherence so long as we are following individual chains of molecular causation. The mutually interpenetrating lines of influence converging upon and issuing from our DNA reveal their full meaning only when we consider what needs and interests are reflected in the overall, coordinated pattern of causes — *what the organism is doing and why*.

WHERE ARE WE NOW?

Gene Expression: A Long and Winding Journey

If you feel exhausted at this point, I will understand. Any effort to fully take hold of life, at any scale of observation and activity, can prove exhausting. The way in which gene expression arises from, or is disciplined by, or is made to serve, all aspects of an organism’s life may be tiring to explore, even in the sorely incomplete manner of the foregoing. But taking note of the basic fact of the matter is well worthwhile. I am not at all tempted to try to summarize anew here the ground we have covered. But I will extract two statements from the text above suggesting one way to view the significance of everything we have looked at:

> (1) Given the play of infinite, interwoven influences at the molecular level, where non-mechanical fluidity rules and the number of actors relevant to just about any function of the cell or organism is unlimited, there seem only two possibilities: complete bedlam and chaos of causes working at cross-purposes, or else the play of an encompassing wisdom whose all-embracing effectiveness and power of coordination we can hardly yet even begin to conceive.
>
> (2) In the plastic organism, what goes on at the local level is always shaped and guided by a larger, coherent context — a context that surely has meaning, but (as in natural languages) never an absolutely fixed grammar or logic.

These conclusions could hardly be more upsetting for a molecular biology centered on theoretical notions of code, informational logic, and discrete causes. We need not only a tracing of physical and chemical lawfulness, but also an understanding of the meaning, end (*telos*), and purposiveness of things — a hard pill to swallow for the conventionally trained biologist. But it’s not as if much imagination is required in order to see which way the current is pulling us in today’s deep-diving explorations of molecular biology.

We had an introduction to epigenetics (as genetics seen in context) in Chapter 7. That, together with this current chapter, as well as much else in the first half of the book will need to be kept in mind as we pass on to the discussion of evolution in the second half of the book. We will see that the main point of the older, outmoded concept of gene expression was to eliminate the life of the organism from evolutionary theorizing. If you remember what you have read here, you will have much less difficulty thinking about how organisms themselves — collectively organized in a species or population — might be the real drivers of evolution, much as the cells and microbiome, collectively in each of us, are so organized as to give adaptive expression to the life of the individual.

Notes

1. In Chapter 8 ("The Mystery of an Unexpected Coherence") we looked at how proteins can rescue completely shattered DNA.

2. The "promiscuity" of binding — that is, binding in the absence of definitive binding sequences — is a problem relating to protein-nucleotide interactions in general. For example, 55 percent of RNA-binding proteins "do not contain any known RNA-binding domain at all" (Editors of *Nature Structural & Molecular Biology* 2021).

3. Figure 14.1 credit: https://regnetworkweb.org/about.jsp

4. I will not discuss the RNA portion of chromatin here. But its importance, which researchers are now struggling to unravel, looks as though it may rival the diverse functions of the protein portion.

5. No contemporary biologist has a sound basis for assuming "necessary contextualization and direction", because the idea of wise direction is foreign to the current presuppositions of biology. But every biologist, in talking about specific molecular processes, nevertheless *does* make the assumption — and makes it for the simple reason that there is no alternative. We either assume the wisely guided context or our immediate work becomes meaningless. It loses its whole point, which is to explain how one or another process contributes to a *function* or *task* — that is, to an effectively directed, purposive activity (Chapter 2). So biologists are forever implicitly placing themselves within a theoretical framework that, from their own standpoint, is indefensible.

6. By "modest-sized" I mean: about 2000 nucleotide bases in length.

7. Figure 14.2 credit: Kazantseva and Palm 2014 under Creative Commons CC-BY license.

8. Figure 14.3 credit: Tóth-Petróczy et al. 2008, editing by Dennis Pietras, Buffalo NY. CC BY-SA 4.0.

9. Here is one paragraph from a paper on the Mediator complex:

> The Mediator is an evolutionarily conserved, multiprotein complex that is a key regulator of protein-coding genes. In metazoan cells, multiple pathways that are responsible for homeostasis, cell growth and differentiation converge on the Mediator through transcriptional activators and repressors that target one or more of the almost 30 subunits of this complex. Besides interacting directly with RNA polymerase II, Mediator has multiple functions and can interact with and coordinate the action of numerous other co-activators and co-repressors, including those acting at the level of chromatin. These interactions ultimately allow the Mediator to deliver outputs that range from maximal activation of genes to modulation of basal transcription to long-term epigenetic silencing (Malik and Roeder 2010).

Mediator also has tissue-specific aspects:

> Adding yet another degree of complexity, members of the same transcription factor family can target different Mediator subunits to activate transcription of the same gene, through the same promoter elements, in different cell types (Conaway and Conaway 2011).

10. Figure 14.4 credit: Quevedo et al. (2019). CC BY-SA 4.0.

11. Figure 14.5 credit: courtesy of David S. Goodsell and RCSB Protein Data Bank.

12. The Wikipedia article, “Tata-binding protein” (accessed on April 1, 2019), offers a succinct description of part of this interaction: “When TBP binds to a [particular sequence] within the DNA, it distorts the DNA by inserting amino acid side-chains between base pairs, partially unwinding the helix, and doubly kinking it. The distortion is accomplished through a great amount of surface contact between the protein and DNA. TBP binds with the negatively charged phosphates in the DNA backbone through positively charged lysine and arginine amino acid residues. The sharp bend in the DNA is produced through projection of four bulky phenylalanine residues into the minor groove. As the DNA bends, its contact with TBP increases, thus enhancing the DNA-protein interaction.”

13. There are actually three RNA polymerase enzymes in humans: RNA polymerase I, II, and III. I will be speaking of RNA polymerase II, which transcribes the great majority of our genes. Also, “RNA” in the following descriptions will refer either to messenger RNA (mRNA), which can be translated into protein, or else to RNA more generally. References to specific non-protein-coding RNAs such as microRNAs (miRNAs) will be flagged as such.

14. Just about any functional significance of an RNA — from what protein it produces, to its stability and cellular localization, to the various roles of its three-dimensional structure — can be affected by this editing. One kind of editing (known as A-to-I editing) “is extremely abundant in primates: over a hundred million editing sites exist in [RNAs derived from] their genomes” (Levanon and Eisenberg 2014). However, biologists have only begun to explore the functional significance of most of this editing, and there remains among the majority of researchers today a tendency to dismiss as “random noise” whatever their current methods and concepts cannot presently illuminate.

15. Frye 2018. Regarding one of these modifications, known as mRNA adenosine methylation (m^6A), Timothy Nilsen, a molecular biologist at Case Western Reserve University in Cleveland, has written:

> A series of papers have appeared in rapid succession, together providing a wealth of unequivocal evidence for m^6A function. But these findings still have not led to a coherent picture of the number and variety of functions of the m^6A modification (Nilsen 2014).

In the several years since he wrote that, the picture has, bit by bit, been filled in, and continues to be filled in. But there is a long way to go.

16. Figure 14.6 credit: From Tay, Rinn and Pandolfi (2014).

17. Figure 14.6 is extremely simple. The authors of the paper from which the figure is drawn refer to a study of brain cancer (glioblastoma) where “the analysis was significantly extended beyond the binary ceRNA associations described in most other studies”, and “the PTEN ceRNA interactions were found to be part of a post-transcriptional regulatory layer comprising more than 248,000 microRNA-mediated interactions”.

18. Of course, anything can be analyzed in one way or another if we narrow our vision sufficiently and disregard, for example, the purposive (*telos*-realizing) aspects of what is going on. The question is whether analyzing living activity by breaking it into physically explicable part-processes yields an explanation or understanding of its *telos*-realizing character. Throughout this book I have been pointing out the incommensurability between a strictly physical analysis of biological phenomena and the recognizable *meaning* of those phenomena.

19. Figure 14.7 credit: Ada Olins and Donald Olins, University of Tennessee/Oak Ridge Graduate School of Biomedical Sciences.

20. An example of the functioning of linker histones: "Our results establish H1 as a critical regulator of gene silencing through localized control of chromatin compaction, 3D genome organization and the epigenetic landscape" (Willcockson et al. 2020).

The functions of the linker histone are also indicated by the fact that "mutations in H1 drive malignant transformation primarily through three-dimensional genome reorganization, which leads to epigenetic reprogramming and derepression of developmentally silenced genes" (Yusufova et al. 2020). And then there is this: "The biochemical functions of H1 in the regulation of nuclear DNA metabolism should not be limited to a single, one-size-fits-all DNA compaction paradigm. Rather, H1 appears to be an active biochemical player in chromatin and a potent effector of multiple aspects of chromosome structure and chromatin functions" (Fyodorov 2018).

21. Figure 14.8 credit: Darekk2, CC BY-SA 3.0, via Wikimedia Commons (own work).

22. Figure 14.9 credit: Fyodorov et al. 2017.

23. Figure 14.10 credit: Darekk2 (CC BY-SA 3.0) based on data from the Protein Data Bank.

24. Figure 14.11 credit: Luger 2006.

25. Figure 14.12 credit: Zygote Media Group (CC BY 2.5) via Wikimedia Commons.

Sources

Berger, Shelley L. (2007). "The Complex Language of Chromatin Regulation during Transcription", *Nature* vol. 447 (May 24), pp. 407-12. doi:10.1038/nature05915

Bissell, Mina (2011). "Why Don't We Get More Cancer? A Proposed Role of the Microenvironment in Restraining Cancer Progression", *Nature Medicine* vol. 17, no. 3 (March), pp. 320-29. doi:10.1038/nm.2328

Bobola, Nicoletta and Samir Merabet (2017). "Homeodomain Proteins in Action: Similar DNA Binding Preferences, Highly Variable Connectivity", *Current Opinion in Genetics and Development* vol. 43 (April), pp. 1-8. doi:10.1016/j.gde.2016.09.008

Brown, Valerie (2008). "Environment Becomes Heredity", *Pacific Standard* (July 14). https://psmag.com/nature-and-technology/environment-becomes-heredity-4425

Cairns, Bradley R. (2009). "The Logic of Chromatin Architecture and Remodelling at Promoters", *Nature* vol. 461 (September 10), pp. 193-98. doi:10.1038/nature08450

Chaires, Jonathan B. (2008). "Allostery: DNA Does It Too", *ACS Chemical Biology* vol. 3, no. 4 (April 18), pp. 207-9. doi:10.1021/cb800070s

Conaway, Ronald C. and Joan Weliky Conaway (2011). “Function and Regulation of the Mediator Complex”, *Current Opinion in Genetics and Development* vol. 21, pp. 225-30. doi:10.1016/j.gde.2011.01.013

Cosgrove, Michael (2012). “Writers and Readers: Deconvoluting the Harmonic Complexity of the Histone Code”, *Nature Structural and Molecular Biology* vol. 19, no. 8 (August), pp. 739-40. doi:10.1038/nsmb.2350

Editors of *Nature Molecular & Structural Biology* (2021). “The Nucleotides That Bind”, *Nature Structural & Molecular Biology* vol. 28, no. 1 (January). doi:10.1038/s41594-020-00552-8

Frye, Michaela, Bryan T. Harada, Mikaela Behm and Chuan He (2018). “RNA Modifications Modulate Gene Expression during Development”, *Science* vol. 361, no. 6409 (September 28), pp. 1346-49. doi:10.1126/science.aau1646

Fuchs, Gilad and Moshe Oren (2014). “Writing and Reading H2B Monoubiquitylation”, *Biochimica et Biophysica Acta* vol. 1839, pp. 694–701. doi:10.1016/j.bbagrm.2014.01.002.

Fyodorov, Dmitry V., Bing-Rui Zhou, Arthur I. Skoultchi and Yawen Bai (2017a). “Emerging Roles of Linker Histones in Regulating Chromatin Structure and Function”, *Nature Reviews Molecular Cell Biology* vol. 19 (March), pp. 192-206. doi:10.1038/nrm.2017.94

Gan, Qiong, Tadashi Yoshida, Oliver G. McDonald et al. (2007). “Concise Review: Epigenetic Mechanisms Contribute to Pluripotency and Cell Lineage Determination of Embryonic Stem Cells”, *Stem Cells* vol. 25, no. 1, pp. 2-9. doi:10.1634/stemcells.2006-0383

Fyodorov, Dmitry V., Bing-Rui Zhou, Arthur I. Skoultchi and Yawen Bai (2018). “Emerging Roles of Linker Histones in Regulating Chromatin Structure and Function”, *Nature Reviews Molecular Cell Biology* vol. 19, no. 3 (March), pp. 192-206. doi:10.1038/nrm.2017.94

Gillooly, James F., Andrew Hein and Rachel Damiani (2015). “Nuclear DNA Content Varies with Cell Size across Human Cell Types”, *Cold Spring Harbor Perspectives in Biology* 2015;7:a019091 (July). doi:10.1101/cshperspect.a019091

Hill, Meredith and Nham Tran (2021). “Global miRNA to miRNA Interactions: Impacts for miR-21”, *Trends in Cell Biology* vol. 31, no. 1, pp. 3-5. doi:10.1016/j.tcb.2020.10.005

Hinde, Elizabeth, Francesco Cardarelli, Aaron Chen et al. (2012). “Tracking the Mechanical Dynamics of Human Embryonic Stem Cell Chromatin”, *Epigenetics and Chromatin* vol. 5, no. 20. doi:10.1186/1756-8935-5-20

Joshi, Sachindra R., Yaw C. Sarpong, Ronald C. Peterson and William M. Scovell (2012). “Nucleosome Dynamics: HMGB1 Relaxes Canonical Nucleosome Structure to Facilitate Estrogen Receptor Binding”, *Nucleic Acids Research* vol. 2012, pp. 1-11. doi:10.1093/nar/gks815

Kazantseva, Jekaterina and Kaia Palm (2014). “Diversity in TAF Proteomics: Consequences for Cellular Differentiation and Migration”, *International Journal of Molecular Sciences* vol. 15, no. 9 (September 19), pp. 16680-97. doi:10.3390/ijms150916680

Klerk, Eleonora de and Peter A. C. ’t Hoen (2015). “Alternative mRNA Transcription, Processing, and Translation: Insights from RNA Sequencing”, *Trends in Genetics* vol. 31, no. 3 (March), pp. 128-39. doi:10.1016/j.tig.2015.01.001

Kristjánsdóttir, Katla, Elizabeth A. Fogarty and Andrew Grimson (2015). “Systematic Analysis of the *Hmga2* 3’ UTR Identifies Many Independent Regulatory Sequences and a Novel Interaction Between Distal Sites”, *RNA* vol. 21, no. 7 (July), pp. 1346-60. https://rnajournal.cshlp.org/cgi/doi/10.1261/rna.051177.115

Kwak, Hojoong and John T. Lis (2013). “Control of Transcriptional Elongation”, *Annual Review of Genetics* vol. 47, pp. 483-508. doi:10.1146/annurev-genet-110711-155440

Lai, William K. M. and B. Franklin Pugh (2017). “Understanding Nucleosome Dynamics and Their Links to Gene Expression and DNA Replication”, *Nature Reviews Molecular Cell Biology* vol. 18, pp. 548-62. doi.org/10.1038/nrm.2017.47

Levanon, Erez Y. and Eli Eisenberg (2014). "Does RNA Editing Compensate for Alu Invasion of the Primate Genome?", *Bioessays* vol. 37, pp. 175–81. https://doi.wiley.com/10.1002/bies.201400163

Lodato, Michael A., Mollie B. Woodworth, Semin Lee et al. (2015). "Somatic Mutation in Single Human Neurons Tracks Developmental and Transcriptional History", *Science* vol. 350, no. 6256 (October 2), pp. 94-98. doi:10.1126/science.aab1785

Luger, Karolin (2006). "Dynamic Nucleosomes", *Chromosome Research* vol. 14, pp. 5-16. doi:10.1007/s10577-005-1026-1

Makowski, Matthew M., Guillaume G. Aullier and Karolin Luger (2020). "Picking a Nucleosome Lock: Sequence- and Structure-Specific Recognition of the Nucleosome", *Journal of Biosciences* vol. 45, article 13. doi:10.1007/s12038-019-9970-7

Malik, Sohail and Robert G. Roeder (2010). "The Metazoan Mediator Co-Activator Complex as an Integrative Hub for Transcriptional Regulation", *Nature Reviews Genetics* vol. 11 (November), pp. 761-72. doi:10.1038/nrg2901

Martinez-Campa, Carlos, Panagiotis Politis, Jean-Luc Moreau et al. (2004). "Precise Nucleosome Positioning and the TATA Box Dictate Requirements for the Histone H4 Tail and the Bromodomain Factor Bdf1", *Molecular Cell* vol. 15 (July 2), pp. 69-81. doi:10.1016/j.molcel.2004.05.022

Michieletto, Davide and Nick Gilbert (2019). "Role of Nuclear RNA in Regulating Chromatin Structure and Transcription", *Current Opinion in Cell Biology* vol. 58, pp. 120-25. doi:10.1016/j.ceb.2019.03.007

Miller, Courtney A. and J. David Sweatt (2007). "Covalent Modification of DNA Regulates Memory Formation", *Neuron* vol. 53 (March 15), pp. 857-69. doi:10.1016/j.neuron.2007.02.022

Moretti, Rocco, Leslie J. Donato, Mary L. Brezinski et al. (2008). "Targeted Chemical Wedges Reveal the Role of Allosteric DNA Modulation in Protein-DNA Assembly", *ACS Chemical Biology* vol. 3, no. 4, pp. 220-29. doi:10.1021/cb700258r

Musselman, Catherine A., Marie-Eve Lalonde, Jacques Côte and Tatiana G. Kutaleladze (2012). "Perceiving the Epigenetic Landscape Through Histone Readers", *Nature Structural and Molecular Biology* vol. 19, no. 12 (December), pp. 1218-27. doi:10.1038/nsmb.2436

Mustoe, Anthony M., Charles L. Brooks and Hashim M. Al-Hashimi (2014). "Hierarchy of RNA Functional Dynamics", *Annual Review of Biochemistry* vol. 83, pp. 441–66. doi:10.1146/annurev-biochem-060713-035524

Nilsen, Timothy W. (2014). "Internal mRNA Methylation Finally Finds Functions", *Science* vol. 343 (March 14), pp. 1207-8. doi:10.1126/science.1249340

Quevedo, Marti, Lize Meert, Mike R. Dekker, et al. (2019). "Mediator Complex Interaction Partners Organize the Transcriptional Network That Defines Neural Stem Cells", *Nature Communications* vol. 10, no. 2669. https://doi.org/10.1038/s41467-019-10502-8.

Rohs, Remo, Sean M. West, Alona Sosinsky et al. (2009). "The Role of DNA Shape in Protein-DNA Recognition", *Nature* vol. 461 (October 29), pp. 1248-53. doi:10.1038/nature08473

Separovich, Ryan J., Chi Nam Ignatius Pang, and Marc R. Wilkins (2020). "Controlling the Controllers: Regulation of Histone Methylation by Phosphosignalling", *Trends in Biochemical Sciences*. https://doi.org/10.1016/j.tibs.2020.08.004

Severin, Philip M. D., Xueqing Zou, Hermann E. Gaub and Klaus Schulten (2011). "Cytosine Methylation Alters DNA Mechanical Properties", *Nucleic Acids Research* vol. 39, no. 20, pp. 8740-51. doi:10.1093/nar/gkr578

Slattery, Matthew, Tianyin Zhou, Lin Yang et al. (2014). "Absence of a Simple Code: How Transcription Factors Read the Genome", *Trends in Biochemical Sciences* vol. 39, no. 9 (September), pp. 381-99. doi:10.1016/j.tibs.2014.07.002

Talbott, Stephen L. (2021). "How the Organism Decides What to Make of Its Genes". https://bwo.life/org/support/genereg.htm

Tay, Yvonne, John Rinn and Pier Paolo Pandolfi (2014). "The Multilayered Complexity of ceRNA Crosstalk and Competition", *Nature* vol. 505 (January 16), pp. 344-52. doi:10.1038/nature12986

Tóth-Petróczy, Ágnes, Christopher J. Oldfield, István Simon et al. (2008). “Malleable Machines in Transcription Regulation: The Mediator Complex”, *PLOS Computational Biology* (December 19). doi.org/10.1371/journal.pcbi.1000243

Turner, Bryan M. (2014). “Nucleosome Signalling: An Evolving Concept”, *Biochimica et Biophysica Acta* vol. 1839, pp. 623-26. doi:10.1016/j.bbagrm.2014.01.001

Wang, lishi, Hongchao Liu, Yan Jiao et al. (2015). “Differences between Mice and Humans in Regulation and the Molecular Network of Collagen, Type III, Alpha-1 at the Gene Expression Level: Obstacles that Translational Research Must Overcome”, *International Journal of Molecular Sciences* vol. 16, no. 7 (July), pp. 15031-56. doi:10.3390/ijms160715031

Wei, Jiufeng, Guodong Li, Shuwei Dang et al. (2016). “Discovery and Validation of Hypermethylated Markers for Colorectal Cancer”, *Disease Markers* vol. 2016. doi:10.1155/2016/2192853

Willcockson, M. A., S. E. Healton, C. N. Weiss et al. (2020). "H1 Histones Control the Epigenetic Landscape by Local Chromatin Compaction”, *Nature* (December 9). https://doi.org/10.1038/s41586-020-3032-z

Woelfle, Mark A., Yao Xu, Ximing Qin et al. (2007). “Circadian Rhythms of Superhelical Status of DNA in Cyanobacteria”, *PNAS* vol. 104, no. 47, pp. 18819-24. doi:10.1073/pnas.0706069104

Yusufova, Nevin, Andreas Kloetgen, Matt Teater et al. (2020). “Histone H1 Loss Drives Lymphoma by Disrupting 3D Chromatin Architecture”, *Nature* (December 9). https://doi.org/10.1038/s41586-020-3017-y

CHAPTER 15

Puzzles of the Microworld

A mouse and an elephant live in fundamentally different physical worlds so far as their own spatial dimensions and their relation to the force of gravity are concerned. The fact is evident enough in the way mice scurry around, darting this way and what, while the elephant carries its weight more slowly and deliberately. Or, to approach the matter from a very different direction: if you dropped a mouse from seven meters (twenty-three feet) above a meadow, it would likely right itself after landing and scamper away. If you dropped an elephant from that height, it would die from massive internal trauma. And if you simply left a beached blue whale where it lay, it might die from any of several different causes, one of which is being crushed under its own weight. All this has to do with the changing relation between the weight of an animal and the surface area of its body as its overall size changes.[1]

So when we talk about the diverse environments in which organisms live, one aspect of the diversity has to do with their varying experiences of the force of gravity in relation to the dimensional aspects of their lives. To be a different size is already to live in a different world.

Einstein, so it is said, was led to his theory of special relativity due in part to his having imagined what it would be like to “ride on a light beam”. Might we possibly discover equally strange things if we tried to imagine what it would be like to dwell within an individual living cell?

Unlike Einstein with his task, ours would be much simpler. It would not require bold new understandings in physics, but simply a willingness to imagine the changing play, at different dimensions, of already formulated physical laws. And, fortunately, we have at least one scientific paper, written thirty years ago, that has already done much of the work of imagining the startlingly different conditions of life at the scale of the cell.

That 1990 paper was written by Guenter Albrecht-Buehler of the Northwestern University Medical School in Chicago. He began his professional life as a physicist before moving into cell biology. However, unlike what you might expect of a physicist, one of his larger concerns was rooted in the conviction that we cannot build up an understanding of organisms by starting from the molecular level. His paper, titled “In Defense of ‘Nonmolecular’ Cell Biology”, has not, in my judgment, received the attention it deserves. The present chapter represents my effort to summarize only that part of the paper dealing with the wildly unexpected consequences of differences of scale, and then to offer a few additional comments of my own.

Unless otherwise indicated, quotes in the following section are drawn from Albrecht-Buehler’s paper.

Warning: This chapter is a bundle of contradictions. In fact, that is more or less its point. The ways we think and speak about the submicroscopic world are almost guaranteed to be impossibly off the mark, and yet anyone who would point this out has no choice but to use the established, off-the-mark language, which is the only language we currently have available. So if you begin to notice a jarring dissonance between the intended meaning and the actual language of particular statements — and I hope you will — you can take it as a sure sign that you are getting the point of the chapter.

For example, you will hear me saying that "If you considered two isolated electrons to be point masses and placed them 1 meter apart …" You will likewise hear me talking about the "collisions" of "particles", and you will listen to a prominent cell biologist remarking how the 5 billion proteins in a cell are "jammed shoulder to shoulder, [while] also charging past one another at insanely high speeds". These references to "isolated electrons", "point masses", "collisions", and "proteins charging past one another" all seem to demand that we imagine particular *things* acting in the manner of the familiar objects of our experience.

But, as I hope you will realize by the end of the piece, there are no *things* of that sort "down there". What *is* down there is a very good question. And if you are asking it by the time you finish reading this, then the chapter will have accomplished its purpose.

From here to there — or, down the rabbit hole?

Albrecht-Buehler begins his main discussion by remarking that the size of cells "is so dramatically much smaller than the macroscopic objects we are accustomed to judging, that it is fair to say they live in an utterly alien world". The surface-to-volume ratio of a cell — a crucial consideration underlying the mouse–elephant comparison above — is 100,000 times greater for a typical cell-sized sphere than for an everyday-sized sphere with a diameter of 50 centimeters (about 20 inches). But the "alien" character we discover by imagining the life of a cell at its own dimensions goes far beyond the principle we learn by dropping mice and elephants to the ground. Nevertheless, that principle isn't a bad place to start.

From wine to jelly. Suppose we shrink a wine bottle to one-tenth its normal size, reducing the 2-centimeter diameter of its neck to 2 millimeters. If we now turn the bottle upside down, nothing pours out. This is, again, due to the changing surface-to-volume ratio as the size of an object (wine bottle) decreases. Given the shrinkage of the bottle, the volume (and therefore the weight) of the wine has decreased much more than the surface area of the air-wine boundary in the bottle's neck. The shaping forces[2] that hold the wine together in one compact mass at that boundary are now too strong for the reduced gravitational weight of wine in the bottle to overcome.

We see the natural tendency of such shaping forces in water when we observe tiny droplets of dew on a waxy leaf. Instead of spreading out over the leaf, the water draws itself into a roughly spherical shape. But if we instead had a ball of water 10 centimeters (4 inches) in diameter and could manage to place it on a flat surface, the water's much greater weight would overwhelm its shaping forces, so that the liquid would flow out in all directions. Only in the tiny droplets that might remain here and there would we again see the spherical, dew-drop shape we are familiar with on leaves, grass blades, and so on.

The point to attend to, then, is that change of size can result in dramatic differences in the play of forces. Of course, our wine bottle's reduction in size was not very great. Reflect now upon the fact that the volume of water in a typical cell is not 10 times, but rather 28,000 times smaller than the volume of a wine bottle. Albrecht-Buehler remarks of the non-flowing wine in the neck of the shrunken wine bottle that it appears to have become rigid, "like jelly". Indeed, "wine can turn into jelly just by existing in smaller amounts". Try to imagine the implications of that statement in light of a scale reduction by a factor of 28,000!

Figure 15.1. A dew droplet on a leaf. The droplet is about one millimeter in diameter.[3]

Viscous drag. A fluid's *viscosity* is a measure of its "thickness", or its internal, frictional resistance to free flow. Molasses is more viscous than water. And the more viscous the fluid, the greater the *drag*, or resistance, it presents to an object moving through it.

Albrecht-Buehler compares the effects of viscous drag upon two objects moving through water — a spherical cell, and a sphere with a 50-centimeter diameter. Both spheres are assumed to consist of the same protein matrix. He asks: If an initial movement of one diameter per second is imparted to both of them, how quickly would they come to a stop due to the resistance of the water? It turns out that the larger sphere will travel long enough to traverse many diameters. By contrast, the cell-sized sphere will stop within about a millionth of a second, during which it will have traveled about a millionth of a diameter — which is more or less to say that it stops immediately and doesn't travel at all.

This might seem to suggest that if you or I lived at the size of a cell — or, worse, a molecule within a cell — and if we wanted to take a swim, we might just as well try swimming inside a large block of concrete. But this can't really be the case, and only illustrates the difficulty of transporting ourselves in imagination to a different scale of existence. Objects like you and I — or pebbles and flowers, or the gears and levers of a machine — could not be scaled down to a sub-cellular level and still remain what they were in any meaningful sense. They would become objects of an entirely different character.

Further, molecules "live" at a radically reduced scale compared to the cell, so in moving from the whole cell to the molecular level (what I will call the "microworld"), we see the various lawful relations changing yet again. In reality, molecules move through their cellular environs (as we will see below) with remarkable speed. Moreover, despite the example above, even cells move quite well in their viscous environment. So still other factors must come into play.

Brownian movement. In 1827 the Scottish botanist, Robert Brown, used a microscope to observe tiny pollen granules, about 5 microns (5 millionths of a meter) long, suspended in water. (For comparison, the diameter of a typical human cell nucleus is about 10 microns.) He observed a continuing series of movements — a “rapid oscillatory motion” — in what appeared to be random directions. Such movements, apparently coming from nowhere, were a considerable mystery at the time.

The motion, which gained the name “Brownian”, was further characterized by later investigators. Their work confirmed three features of the movements: they were indeed random in the sense that all directions were “equally likely”; “further motion seemed totally unrelated to past motion”; and “the motion never stopped”. In addition, “small particle size and low viscosity of the surrounding fluid resulted in faster motion” (Encyclopedia Britannica editors).

In the early twentieth century the French physicist, Jean Baptiste Perrin, recorded the positions of three particles in water at 30-second intervals, as viewed through the microscope. His representation is shown in Figure 15.2.

Today Brownian movement is commonly visualized, however problematically,[5] as being due to random collisions (“random thermal fluctuations”) of a liquid’s molecules with a very small suspended object. In this sense, writes Albrecht-Buehler, the contents both within a cell and in its external, watery environment are “jerking violently”. Moreover, these effects outweigh those of gravity to such an extent that collisions with just two to three molecules in a cell’s environment are enough to counterbalance the gravitational weight of the cell, keeping it from sinking in water. Given the countless trillions of such impacts coming from all sides, “another way of formulating this result is to say that gravity is an entirely irrelevant force in the violently chaotic world of cells”.[6]

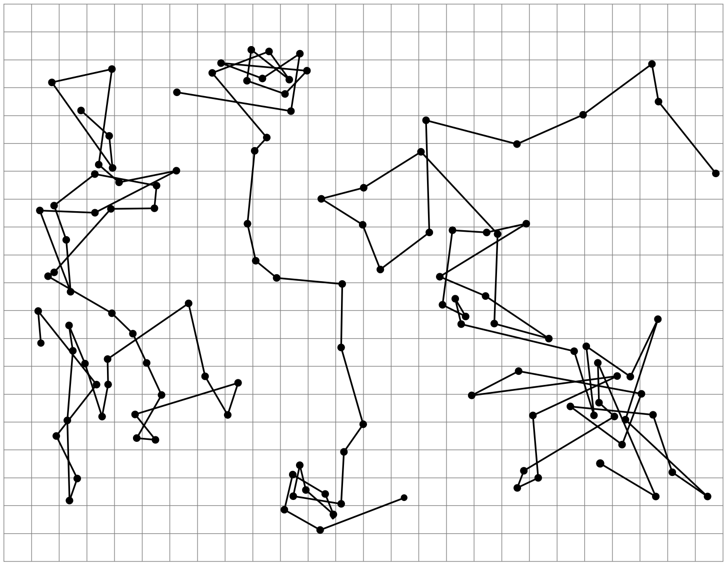

Figure 15.2. Tracings of the motions in water of three colloidal particles of radius 0.53 microns, as seen under the microscope. Successive positions every 30 seconds are joined by straight line segments. The grid lines are 3.2 microns apart. Note that the straight lines are artifacts of the fact that positions were recorded at 30-second intervals. More frequent measurements would have yielded smoother curves (but the overall movement, with its directional changes, might still be termed “jerky”).[4]

Chemical energies. A cell, turbulent as it may seem from some standpoints, is actually far from being an "out-of-control" world. One good reason for this has to do with the chemical bonds between atoms and molecules. Even the weakest (hydrogen) bonds are strong enough to remain stable in the presence of Brownian fluctuations. So the making and breaking of these bonds involves the ordered direction and redirection of vast amounts of energy.

Here is one example of the use of chemical energy. A single muscle cell contains hundreds of subunits ("sarcomeres") whose dimensions are less than 3 millionths of a meter. They contract by converting chemical energy into mechanical energy. The force delivered by one sarcomere, as Albrecht-Buehler remarks, is such that "it can lift 60 entire cells! In other words, the cells submersed in violently jerking molasses of their surrounding aqueous media have literally gigantic forces at their disposal".

Electrical forces. If gravitational forces tend toward complete insignificance at the cellular level, the same can hardly be said of electrical forces. The first thing to realize is how much more powerful than gravity is the electrical force. Here is one way to think about it. If you considered two isolated electrons to be point masses and placed them 1 meter apart, there would be a certain force of gravitational attraction between them. Suppose, then, that you wanted to know where you should place them in order for the magnitude of the electrical force between them (a force of repulsion rather than attraction in this case) to be of the same magnitude as the gravitational force at 1 meter.

The answer is that you would have to separate the electrons by approximately 200,000 light years.[7] This amounts to more than 34 billion times 34 billion miles. This is too much to get one's head around, so the take-home point is simply that the electrical force is inconceivably stronger than the gravitational force.

The remarkable thing is that, in most of our routine experience of the world around us, we would hardly suspect the ubiquitous presence of such monstrous forces relative to our experience of gravity. This has to do with the fact that, in the world we normally experience, the bearers of negative electrical forces, such as electrons, are more or less counterbalanced by bearers of positive electrical forces, such as protons.

The way in which charged particles naturally tend to distribute themselves gets very complex, but the upshot of it all is the following: while the electrical forces between cellular constituents are unthinkably more powerful than the gravitational forces, they don't simply rip the cell to smithereens. Here, too, negative and positive charges tend to balance each other out, but the operative word is "tend". The imbalances that do exist are enough to help account for a lot of what goes on.

Albrecht-Buehler puts the matter this way: in the molecular collectives of cells, "[charged] molecules do not notice each other until they come closer than about one-third of their diameter. Once they are that close, however, they are attracted or repelled with almost irresistible electrical forces". And again: a single electron charge within the typical electric field spanning a nerve membrane “can balance the weight of an entire cell”. He goes on to mention that “cell surfaces contain thousands of electron charges”.

We might also consider, not just static electrical forces, but electrical currents. Michael Persinger, the late Laurentian University (Canada) neuroscientist who investigated bioelectric phenomena in both the brain and the earth’s atmosphere, was looking, not for great differences, but for close parallels between the two widely varying scales. And he found them. But even here the parallels show how differently we must think, for example, of the brain compared to our routine picturing of physiological processes.

For example, the electrical impulse traveling along the axon of a neuron is driven by what might seem to be a trivial action potential of 0.09 volts. But this voltage applies across a 10 nanometer neuronal membrane, which means that it amounts to millions of volts per meter. This is on the order of the action potential of an atmospheric lightning bolt. And the density (amperes per square meter) of the current traveling along the neuronal path is, according to Persinger, “remarkably similar” to the density of the electric current flowing in a lightning bolt.

So the reality looks rather as if our brains are continually “lit up” by countless cascading, lightning-like discharges — perhaps on the order of a billion discharges per second (Persinger 2012).

Polymerization. “One of the strangest forces that we can encounter in the world of cells that has no counterpart in our world are the forces of polymerization”. We came up against polymerization in Chapter 4, where we talked about the various thin filaments forming the cellular cytoskeleton. The filaments are polymers, composed of repeating protein subunits that can be added or removed at the ends of filaments in a dynamic fashion. The process of adding subunits to a polymer is called “polymerization”. When a cell is migrating, some of these filaments are being extended forward (by means of polymerization) in the direction of the migration, thereby facilitating the cell’s movement.

This can happen because the chemical addition of another subunit to a polymer of the cytoskeleton is an energetic process. “The force of the addition of only one [protein] subunit is ten times larger than the weight of a cell!” In theory, therefore, “adding one subunit to a polymer could lift ten cells by the thickness of the subunit”. This tells us a good deal about how cells can move. At the normal scale of our lives we see nothing like this ability of a tiny unit of matter to be chemically joined to others of its kind and thereby to shift material objects (cells) that happen to be billions of times more massive than that tiny unit. (A typical human cell has been estimated to contain several billion protein molecules, in addition to water, lipids, carbohydrates, and all its other contents.)

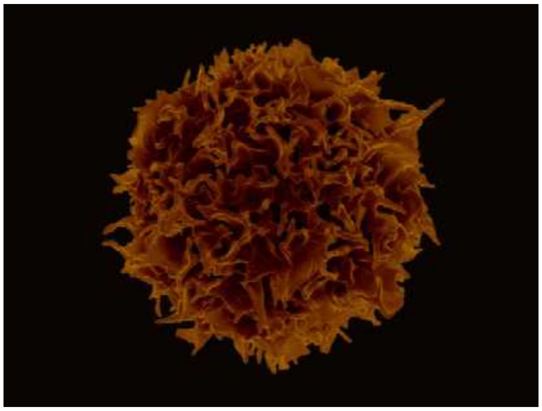

Figure 15.3. Colorized scanning electron micrograph of a T lymphocyte (a kind of immune cell).[8]

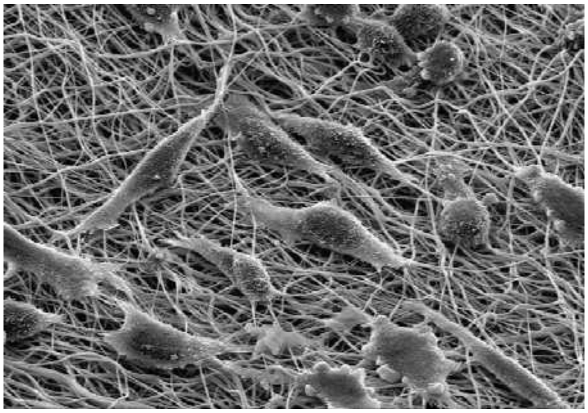

Figure 15.4. Scanning electron microscopy image of mouse fibroblasts cultured on artificial filamentous material.[9]

You will recall from our earlier discussion that a dew drop on a leaf is "pulled" into a sphere by its shaping forces. (See Figure 15.1.) Further, we heard that these forces, relative to the gravitational force that might break the droplet's form and cause it to flow over the flat surface of the leaf, become vastly greater at very small scales. At the level of a cell, one of these shaping forces (surface tension) is "several thousand times larger than the weight of the cell, and we should expect the surface force to shape the cell as a perfect sphere".

The question, therefore, is why a cell is not held rigidly in the shape of a sphere (Figures 15.3 and 15.4). Cells often have all sorts of non-spherical protrusions, and some kinds of cell readily flatten themselves against a surface and slide over it. In doing so, they are overcoming the hugely powerful shaping forces just mentioned. Part of the answer to this particular puzzle is, in Albrecht-Buehler's words, that "the surface forces are no match for the strong polymerization forces". Bundles of cytoskeletal filaments extending in a common direction have no difficulty re-shaping a cell and helping to bring it into movement.

A world hard to get a grip on

How all these unfamiliar elements of the cellular world add up is not easy to picture. And it becomes even less easy when we look at some of the apparent dynamics of cellular life. "Imagine packing all the people in the world into the Great Salt Lake in Utah — all of us jammed shoulder to shoulder, yet also charging past one another at insanely high speeds. That gives you some idea of how densely crowded the 5 billion proteins in a typical cell are."[10]

Those "insanely high speeds" in crowded places are thought to explain how, as a standard textbook puts it, "a typical enzyme will catalyze the reaction of about a thousand substrate molecules every second" — meaning that the enzyme must bind to a new substrate in a fraction of a millisecond. This happens despite the fact that there tend to be relatively few substrate molecules per cell. If, for example, there is only 1 substrate molecule for every 100,000 water molecules, “nevertheless, the active site [the place where catalysis occurs] on an enzyme molecule that binds this substrate will be bombarded by about 500,000 random collisions with the substrate molecule per second”. At the same time, “a large globular protein [like many enzymes] is constantly tumbling, rotating about its axis about a million times per second” (Alberts et al. 2002, pp. 77-78).

As if everything we have heard so far is not difficult enough to comprehend, the problem of imagining microworlds truthfully is greatly magnified by emerging technologies that generate seductive images. When biologists speak so casually of atoms and molecules as *things*, and when engineers then present us with “pictures” of them, we can hardly help taking the pictures as images of actual phenomena. And so they are. But the phenomena we are dealing with are not “down there”. They are “up here”, where we are experiencing our instruments. Those instruments may be telling us *something* truthful about the microworld, but we have to figure out what that something is.

What we derive from “down there” (at the atomic and molecular levels) is mostly mountains of data produced by our instruments. The pictures we look at are representations of that data. If we take these pictures at face value — if we unthinkingly accept them *in the same way* we accept the terms of our visual engagement with the familiar world — then we are projecting into the microworld phenomena that are not actually there.

This is a problem. If images like the one in Figure 15.5 truly represented anything like the physical objects around us, merely reduced to very small dimensions, and if billions of such objects (commonly, if nonsensically, referred to as “molecular machines”) were racing around inside the cell at “insanely high speeds”, tumbling around while rotating a million times per second, they would presumably achieve nothing but rampant destruction within the cell.

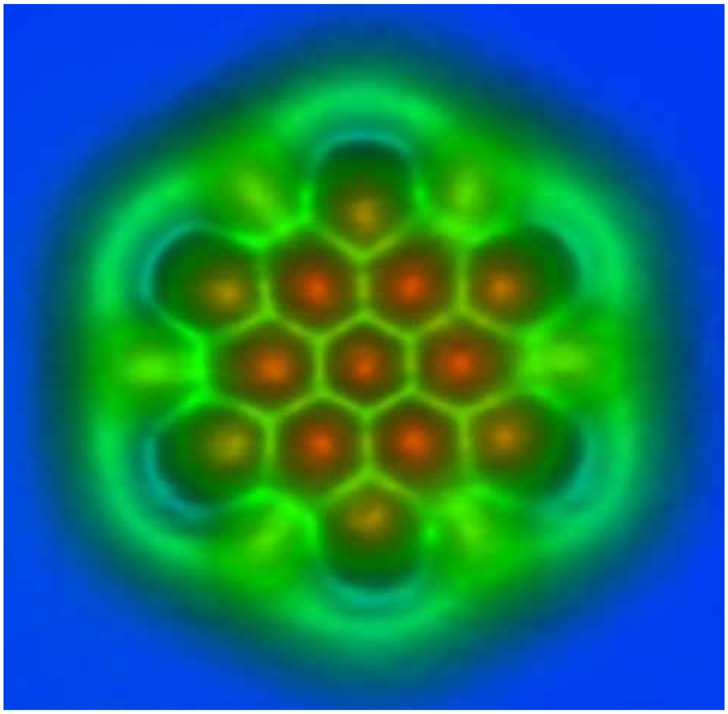

Figure 15.5. An image produced by the interaction of a non-contact atomic force microscope with graphene (a lattice of carbon atoms), in an IBM laboratory. The bright green lines forming approximate hexagons are taken to represent the molecular bonds between carbon atoms.[11]

Figure 15.5, which is said to represent carbon atoms, is not in any normal sense a photograph of atoms, as the scientists and engineers who produce such images well know.

There is no “thing” anywhere in the world that looks like this, except the picture itself. Responsible physicists do not talk about *things* at this level of observation at all. In this particular case we are looking at a kind of colored graph of a data set produced by an atomic force microscope. The spatial distribution of the artificial colors represents the relations between the highly refined measuring instrument, on one hand, and forces at an extremely small (atomic) scale, on the other. It is a picture of a distribution of forces. Forces are not things.

What then?

So what do we make of all the foregoing? It’s hard to say — and maybe that itself is the important point. It is clear enough that when we imagine the world of atoms and molecules in terms of our familiar experience, we are far from truth. If we want some sort of picture, it will hardly do to conjure images of robots or sewing machines or pliers, merely reduced in size (“nanorobots”) and spinning around a million times per second, or a brick beneath a skyscraper receiving an electrical charge and thereby raising the building off the ground, or molecules equivalent to brightly colored baubles.

The one thing we can be sure of is that the cellular realm is not composed of anything like our familiar objects, just made smaller. The really foundational question is whether, and at what scale of observation, we are justified in talking about “things” at all, as opposed to forces or potentials.[12] This question certainly bears on the common appeal by molecular biologists to machine and computer models. As Albrecht-Buehler has written:

> To my knowledge, there is not even a clue as to how to build a liquid miniature computer that would function despite thermal fluctuations and other turbulences in the liquid that would disrupt the circuitry (Albrecht-Buehler 1985).

There is, quite simply, nothing there that could remotely qualify as “circuitry” in the sense of “machine parts”.

One might have thought that the puzzling revelations from our indirect, instrument-mediated encounters with the microworld would have opened up a space for free inquiry as we considered the nature of perceptible, material appearance. One might indeed have expected that — given a realm considered fundamental to our understanding, yet inaccessible to the direct activity of our senses — we might have warned ourselves about the temptation to project falsely imagined perceptual contents into what is in fact an experiential blank for us.

And, given the scientific commitment to empirical (experience-based) evidence, what *are* we to make of a microworld characterized almost solely in terms of thought-models, mathematical formulae, and theoretical constructs, with no sense experience to ground us? Such hoped-for grounding — together with a desire to get beyond the unfettered flights of medieval cerebration — was a good part of the resolve of the pioneers of the Scientific Revolution.

Perhaps we should pick up again from where they started.

Where are we now?

What Does the Microworld Have to Do with Us?

You may be thinking that the topic of this chapter is off the main track of the book. Perhaps so. But then again, just about the entire book is off the main track of the biological sciences today, including molecular biology and (as we will see) evolutionary biology. It is not a bad thing if this chapter encourages us to take note of the limits of our understanding. Nor is it a bad thing if scientists put themselves into a questioning mode rather than the “we understand perfectly well” mode. And certainly it is not a bad thing if, when we look at the inevitable schematic “pictures” of cells in textbooks, we realize how little we understand of what we are looking at.

What we don’t understand goes far beyond the issues discussed in this chapter. The question I have been posing throughout the book is this: Given the wise and well-directed coordination of all the physically lawful life processes we have ever observed, and given the fact that physical lawfulness alone provides no accounting for either the wise coordination or its end-directedness, how can we arrive at a new way of thinking about the problems of life? It hardly seems justified to ignore this question simply because it too easily invites answers that go contrary to our existing intellectual commitments.

In light of such a profound question, it is surely healthy to acknowledge how little our normal habits of thinking allow us to picture what is actually going on at the molecular level where so many have been determined to find their answers. For example, regarding what we have learned in the preceding chapter and Chapter 8 about the regulation of gene expression by countless molecules interacting in a fluid medium, it seems impossible to believe that we currently understand even the most basic truths about how the meaningful coordination of seemingly independent events actually occurs.

If one thing is clear, it is the implausibility of the usual fantasy of molecular-level “machines”. At the very least, we can say that these could have virtually nothing in common with the machines we know of. This means that the most common way of imagining wise and well-directed coordination in the microworld of the organism — by picturing something like the intelligently designed machines of our own making — is a non-starter. Of course, we have already seen (for example, in Chapter 10) many reasons for dismissing the machine-model of organisms, quite apart from those of the current chapter.

Let this be a time for opening our minds rather than sealing them shut. And if the present chapter encourages such opening, so much the better. In any case, we will now move on to evolution. If there is any topic that demands of us an open and questioning mind, it is this one.

Notes

1. As the size of an animal decreases, its volume (and therefore its weight) decreases much more rapidly than its surface area. In other words, as any given object is reduced in size, its surface-to-volume (surface-to-weight) ratio rises. The increased surface-to-weight ratio of the mouse is why its rate of fall is reduced by air resistance more than the elephant's rate of fall. A falling leaf is a more extreme example.

More significantly for the fate of the mouse and the elephant in our rather twisted thought experiment, the different surface-to-weight ratios mean that the weight of the mouse per square centimeter of its body surface striking the ground is minuscule compared to the weight overlying the elephant's area of contact with the ground. So the crushing effect of the impact is much greater for the larger animal.

2. Among the interrelated shaping forces of a liquid such as water are internal cohesion and surface tension.

3. Figure 15.1 credit: Michael Apel, CC BY-SA 3.0, via Wikimedia Commons.

4. Figure 15.2 credit: Original observations made by Jean Baptiste Perrin. Digital rendering by MiraiWarren. Public domain, via Wikimedia Commons.

5. The word "collisions" suggests an activity of *particles* conceived in the manner of our everyday experience of tiny bits of matter. Thinking of water molecules in this way is not something any physicist today would want to defend.

6. It is worth remembering that the lives of large, multicellular organisms — ourselves, for example — are not centered upon the cellular and molecular level. As we walk, run, and otherwise pursue our lives on earth, our bodies must work against the pull of gravity. If we do not sufficiently perform that work — if we are bedridden or live a sedentary life-style — our bodies suffer ill effects.

We know further that the weightlessness endured by astronauts on long missions results in significant loss of bone mass, density, and strength (Keyak 2009). Likewise, lions raised in zoos, apart from the rigors and stresses of hunting and the need to patrol large territories, have a bone structure differing from lions raised in the wild (Holdrege 1998).

So Albrecht-Buehler's assertion that "gravity is an entirely irrelevant force in the violently chaotic world of cells", while it may be true when we are looking at the interplay of forces in the decontextualized cell, can hardly be true for cells in the context of our bodies. If someone experiences changes in bone mass and muscle strength while living in a gravity-free environment, this implies radical changes in cells, including the loss (death) of cells. The fact that, when a person stands upright on earth, the weight of a 150-pound body comes to bear upon the small surface area of two feet certainly makes gravity a "relevant force" for the tissues and cells on the bottoms of our feet. And much the same can be said about the distribution of weight and weight-bearing surfaces throughout our bodies.

Actually, the importance of a larger context was very much part of Albrecht-Buehler's argument in his paper. He was claiming, quite rightly, that we cannot explain either cellular or organismic behavior by trying to ground our picture upon decontextualized molecular-level analyses.

7. I have this answer courtesy of the physicist, George Burnett-Stuart.

8. Figure 15.3 credit: NIAID, CC BY 2.0, via Wikimedia Commons.

9. Figure 15.4 credit: Judyta Dulnik, CC BY-SA 4.0, via Wikimedia Commons.

10. Callier 2021, citing a comparison offered by Anthony Hyman, a British cell biologist and a director of the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden.

11. Figure 15.5 credit: IBM Research–Zurich.

12. Some experimental techniques do give us a form of sense-perceptible report from the microworld. For example, the relatively small "green fluorescent protein" (GFP) can be fused to particular molecules of interest in a cell. When the cell is irradiated with blue or ultraviolet light, the protein fluoresces, revealing under a light microscope the distribution of the target molecules in a cellular location. Again, however, blobs of fluorescent light, while informative of location, do not give us pictures of molecular "objects" residing at that location.

When a student collects a quantity of DNA on a glass rod, she is not looking at DNA molecules, but rather at a white, sticky substance. Similarly, a prospector may be looking at a chunk of iron ore, but he is not examining iron atoms. To say that our instruments, by eliciting responses at an atomic scale, can trace significant structure at that scale, is not to answer in any meaningful experiential sense, "structure of what?" — not if by "what" we refer to objects of the microworld possessing sense-perceptible, material descriptions. We can relate the structure to white, sticky substance or to iron ore, but not to atomic particles imagined in the mode of that substance or that ore.

As a hypothetical question: what would we "see" if, through some sort of inner work, we should develop in the future a cognitive (clairvoyant?) capacity to experience — bring to appearance — whatever can be found, say, at the quantum level? This is, of course, pure speculation. But my surmise is that we would discover an intricately structured play of "forces" of will. We would discover, that is, a field of potential that, when probed in appropriate ways, can be brought to manifestation as materially engaged force. The fact that our own wills (in a manner of which we are completely ignorant and unaware) can take form in the enfleshed mechanical forces of our bodies, while a very different matter, may nevertheless be suggestive in this regard.

Sources

Alberts, Bruce, Alexander Johnson, Julian Lewis et al. (2002). *Molecular Biology of the Cell*, 4th edition, pp. 75-76. New York: Garland Science.

Albrecht-Buehler, Guenter (1985). "Is Cytoplasm Intelligent Too?", chapter 1 in *Cell and Muscle Motility*, edited by Jerry W. Shay, pp. 1-21. Boston: Springer.

Albrecht-Buehler, Guenter (1990). "In Defense of 'Nonmolecular' Cell Biology", *International Review of Cytology* vol. 120, pp. 191-241. doi:10.1016/S0074-7696(08)61601-0

Callier, Viviane (2021). “A Newfound Source of Cellular Order in the Chemistry of Life”, *Quanta Magazine* (January 7). https://www.quantamagazine.org/molecular-condensates-in-cells-may-hold-keys-to-lifes-regulation-20210107/

Encyclopedia Britannica editors, “Brownian Motion”. https://www.britannica.com/science/Brownian-motion. Downloaded January 27, 2021.

Holdrege, Craig (1998). “Seeing the Animal Whole: The Example of the Horse and Lion.” In *Goethe’s Way of Science*, edited by David Seamon and Arthur Zajonc. Albany: SUNY Press, pp. 213-32.

Keyak, J. H., A. K. Koyama, A. LeBlanc, Y. Lu and T. F. Lang (2009). “Reduction in Proximal Femoral Strength Due to Long-Duration Spaceflight,” *Bone* vol. 44, no. 3, pp. 449-53. doi:10.1016/j.bone.2008.11.014

Persinger, Michael A. (2012a). “Brain Electromagnetic Activity and Lightning: Potentially Congruent Scale-Invariant Quantitative Properties”, *Frontiers in Integrative Neuroscience* vol. 6, article 19 (May). doi:10.3389/fnint.2012.00019

CHAPTER 16

Let’s Not Begin With Natural Selection

Evolutionary theorists tend to become frustrated when many of the rest of us fail to “get” the revolutionary and convincing simplicity of natural selection, that primary engine of adaptive evolution also known as “the survival of the fittest”. For example, Niles Eldredge, a paleontologist and, for several decades, a curator at New York’s Museum of Natural History, has wondered, “Why do physicists, who have the reputation of being among the best and the brightest, have such a hard time with the simple notion of natural selection? For simple it is”. He then quotes Charles Darwin:

> As many more individuals of each species are born than can possibly survive; and as, consequently, there is a frequently recurring Struggle for Existence, it follows that any being, if it vary however slightly in any manner profitable to itself, under the complex and sometimes varying conditions of life, will have a better chance of surviving, and thus be *naturally selected*.

“The concept”, Eldredge writes, “is definitely simple enough. This description of natural selection may be a bit longer than the elegantly brief F=MA [force equals mass times acceleration — Newton’s second law of motion]. Conceptually, however, it is hardly more complicated” (Eldredge 2000, pp. 89-90).

The simplicity of what is being promulgated as “natural selection” can hardly be doubted. In his landmark book on *The Nature of Selection*, the philosopher of evolutionary theory, Elliott Sober, considered it “remarkable that a hypothesis of such explanatory power could be so utterly simple conceptually: If the organisms in a population differ in their ability to survive and reproduce, and if the characteristics that affect these abilities are transmitted from parents to offspring, then the population will evolve” (Sober 1984, pp. 21-22).

The idea of natural selection seems to many so straightforward and conclusive that it forces its way into the receptive mind without much need for evidence. August Weismann, whose importance for nineteenth-century evolutionary theory has been considered second only to Darwin’s, rather famously wrote in 1893 that we must accept natural selection as the explanation for the wondrous adaptation of organisms to their environments “because it is the only possible explanation we can conceive”.

Further, according to Weismann, “it does not matter” whether we can demonstrate the role of natural selection in particular cases. “Once it is established that natural selection is the only principle which has to be considered, it necessarily follows that the facts can be correctly explained by natural selection” (quoted in Gould 2002, p. 202).

The compelling simplicity of natural selection, according to Ernst Mayr, is so pronounced as to have proven a stumbling block for many. Mayr, whose influential career spanned the entire twentieth-century history of the modern evolutionary synthesis, proposed that “startling simplicity was the most formidable obstacle that the selection theory had to overcome. Students of the phenomena of life found it undignified to explain progress, adaptation, and design in nature in so mechanistic a manner” (Mayr 1964, p. xviii).

Brief summary statements of the simple logic of natural selection abound. In philosopher Daniel Dennett's succinct formulation, "evolution will occur whenever and wherever three conditions are met: replication, variation (mutation), and differential fitness (competition)" (quoted in Lenski et al.). Or, expanding the idea just a little, we might say that evolution is guaranteed to occur under three conditions:

- There must be trait *variation* among individuals in a breeding population. Without variation, nothing new could ever come about.
- This variation must to some degree be *inherited*, so that offspring generally resemble their parents more than they resemble others. (This is Dennett's principle of *replication*.) If offspring didn't tend to resemble their parents, then it's not clear how variants, even if they occurred, could become established in the larger population.
- Individuals possessing different variants of a trait must, at least in some cases, exhibit *differential fitness* (or differential survival) — that is, they must produce, on average, different numbers of offspring, whether immediate offspring or later descendents. This is often referred to as the principle of *competition* or *survival of the fittest*. The advantage of the fittest organisms is what gives them a better chance of surviving and contributing their fit genes to the descendent population.

With various terminological variations, that is how natural selection is presented in numberless textbooks. According to the influential popularizer (and noted theorist) of evolutionary theory, Stephen Jay Gould, the basic idea has the simplicity of a syllogism. He referred to it as the "syllogistic core" of natural selection (Gould 2002, pp. 125-26n). For Dennett, this core is a "mindless" recipe, or *algorithm*, — one so obvious and universal that it could be derived even without reference to organisms, while nevertheless offering "guaranteed results" in biology. The algorithm is "Darwin's dangerous idea", and it is the key to making sense of everything from the simplest irritable cell to human meaning, cognition, culture, and morality (Dennett 1995, pp. 51, 163-81).

Variation, inheritance, and survival of the fittest: for a certain mindset (well-established in our day), something does indeed seem irresistible and self-evident about the way these conditions testify to the idea of change. And — Eldredge's obtuse physicists apart — more than enough students of evolution do seem smart enough to "get" the extraordinary power and simplicity of natural selection. The widely read British psychologist and science writer, Susan Blackmore, speaks for many when she says that "evolution is inevitable — if you have information that is copied with variation and selection then you *must* get [quoting Dennett] 'Design out of chaos without the aid of mind'". Blackmore goes on almost rapturously: "It is this inevitability that I find so delightful — the evolutionary algorithm just *must* produce design, and once you understand that[,] you have no need to *believe* or not believe in evolution. You see how it works" (Blackmore 2014).

This cocksureness about the simplicity, universality, and persuasive force of the evolutionary algorithm as an explanation for the complex forms of life we observe seems to know no bounds. It extends, for example, even (or especially) to the artificial intelligence community. In 2003 Christoph Adami, who was then head of the Digital Life Laboratory at the California Institute of Technology, defended the value of trivially simple and non-living "digital organisms" — bits of computer code representing genes and living processes — for teaching us about evolution. The principles of evolutionary theory, he said, are "very, very general, and very simple", so that our predictions "don't depend on these little details of molecular biology" (quoted in O'Neill 2003).

It is, we may sense with a certain unease, almost as if actual phenomena become irrelevant to the researcher, who needs only to work out a simple logic.

And our sense of unease only grows when we hear Richard Dawkins discussing how some animals cleverly coerce the behavior of others. For anyone skeptical of his explanation, Dawkins had this word of encouragement: "With natural selection working on the problem, who would be so presumptious as to guess what feats of mind control might not be achieved?" (Dawkins 2008, p. 71). One almost hears an echo of the parent trying to soothe a child's perplexity about some puzzle of creation: "Surely God could do it".

And, indeed, over-estimation of the explanatory power of natural selection may be why Darwin's contemporary, the geologist Charles Lyell, accused him of "deifying" the theory.[1] A century later, in 1971, Lila Gatlin, a biochemist and mathematical biologist who figured centrally in developing the conception of life as an "information processing system", could summarize contemporary usage by saying, "the words 'natural selection' play a role in the vocabulary of the evolutionary biologist similar to the word 'God' in ordinary language" (quoted in Oyama 2000a, p. 31). Such is the power of logical constructions over the human mind.

No doubt the "evolutionary algorithm" truly is simple, and its logic, as far as it goes, is self-evident. But we might want to keep in mind how thin and unstable is the strip of intellectual real estate between "self-evident" and "vacuous" — especially when we find ourselves preferring abstract logical necessity and simplicity to "little details", such as the difference between a computer program and the life of a tiger or octopus.

What are the "guaranteed results" of natural selection?

It is perhaps understandable that the simplistic, if rather hollow, logic of the evolutionary algorithm should be mistaken by some for great explanatory power. In order to assess that power, I would begin by inserting two question marks in what we have just heard. First, there is Darwin's decisively influential remark that "any being, if it vary however slightly in any manner profitable to itself, under the complex and sometimes varying conditions of life, will have a better chance of surviving, and thus be *naturally selected*".

I would insert my main question mark at the word "vary". Notice how easily the word is slipped into the flow of thought, as if it were wholly unproblematic. But variation is the result of the unsurveyable complexity of organic processes — processes that are insistently expressive of a particular organism's way of life and characteristically future-oriented and directive in nature, as when a zygote develops in an adaptive manner into a mature trout or mountain goat.

Yet nothing in Darwin's statement leads one to dwell even for a few seconds on the actual life processes covered by the word "vary". It is as if variation were just something that "happens" to organisms for no particular reason. Taking this happening in an unreflective way ("*Of course* organisms vary!") is a prerequisite for our construing Darwin's words as wonderfully explanatory of the logic of evolution. We don't need to ask ourselves, "How is it that an organism manifests those extraordinary and ubiquitous powers of development, physiology, and behavior, through which variation comes about?"

We heard, in the second place, Elliott Sober marveling at the "explanatory power" of a simple proposition: "if the organisms in a population differ in their ability to survive and reproduce, and if the characteristics that affect these abilities are transmitted from parents to offspring, then the population will evolve." Well, in what sense "evolve"? How does the claim change its persuasive shape when we call to mind that huge numbers of species in the history of life on earth have at some point "evolved" toward extinction?

Those are my two preliminary question marks. But there is much more to say.

To begin with, Sober's claim is strange, given that it is flatly false — false in the sense that nothing in the logic of the theory tells us that populations *must* evolve in a manner that yields new species or fundamental changes of "type". We know that healthy populations do exhibit plasticity, variation, and adaptability — a spruce tree growing in the lowlands will differ greatly from one growing near the alpine treeline, and one tree will differ from its neighbor — but this variability does not by itself imply the evolutionary origin of the diverse forms of life on earth.

For millennia *all* species were widely assumed to remain constant according to their "essential" nature. Certainly untypical variation, including "monstrosities", could occur, but this only reminded our ancestors that defective organisms tended to be removed — part of the means by which the character of the species was preserved. So how did we learn that the situation was quite otherwise, and that species *did* evolve?

Surely the largest factor was the discovery and systematic investigation of fossils. Seeing was believing. It was the apparent historical record, not the logic of natural selection, that settled the question for us. Look at it this way: everything depends on what organisms actually *do* — and, as has long been recognized, one of the most remarkable things they are capable of doing is to give consistent, generation-by-generation expression to the character of their own kind. Whether that kind needed to be understood as a static or dynamic reality could only be resolved through empirical investigation.

Moreover, once we see that species have in fact evolved, we are still left with the most basic questions about how they have done so:

- What sorts of directionality, if any, will we discover in evolutionary change? For example, might change be directed toward more complex or less complex forms of life? Toward greater individuality or more collective interdependence? Toward some sort of diversity, balance, and qualitative completeness upon the earth as a whole? Toward the realization of human potentials?

- What pathways of change are open to any given species at a particular time, and what pathways are closed off by the character of the organisms themselves or of the surrounding world?
- In what ways will molecular and physiological processes be conserved in different organisms during evolution, and in what ways will they diverge?
- How much convergent evolution should we expect? (“Convergent evolution” refers to the independent development of similar features in distinct branches of the “tree of life” — something now known to be strikingly common, as when the “camera-eyes” of the octopus and of humans developed independently of each other.)
- How much diversity of life should we expect, and how radically disparate are the possible forms of life?
- Is evolutionary change more or less possible today than at various times in the past?
- Do populations evolve sporadically or continuously, and why?
- What accounts for the uncanny *qualitative* unity of an organism — a unity leading one observer to say of the sloth, for example, that “every detail speaks ‘sloth’” (Chapter 12).

I can think of no fundamental question about evolution whose answer *is* suggested by the advertised formula for natural selection. Everything depends on what the amazingly diverse sorts of organism actually do as they respond to and shape their environments. Contrary to Susan Blackmore’s exultant insight, nothing in the “algorithmic logic” of natural selection tells us that evolution *must* have happened — and, given that it has happened, the logic by itself tells us little about what we should expect to find in the fossil record. We may ask then, “What, in truth, is being celebrated as the revolutionary principle of natural selection?”

None of this is to deny the trivial validity of the idea of natural selection. *Of course* organisms that are “fitter” will generally do better in life than “unfit” organisms. That’s how we define “fit”. And *of course* a record of the winners and losers in the “struggle for survival” will tell us a great deal about evolutionary processes. Or *could* tell us if we understood all that happened in order to establish this particular record. It is hardly unreasonable to point out that we will gain a profound understanding of evolution only when we know a fair amount about *how* it has happened among actual organisms and along its broad course down through the ages.

Every organism’s life and death encompasses and, so to speak, “sums up” a vast range of purposive activities, not only on its own part, but also on the part of many other organisms. One might feel, therefore, that the “theory” of the survival of the fittest can explain just about everything. Certainly the overall pattern of births and deaths must yield the observed evolutionary outcome! Actually, it just *is* that outcome — it is the pattern we need to explain — which doesn’t yet give us much of a theory.

The "algorithm" of natural selection is widely treated as if it were an agent

The miracle of it all is that, if current evolutionary rhetoric is to be believed, the empty formula of natural selection explains just about everything you could imagine — all based, as this rhetoric consistently informs us, on some form of "blind" agency. Natural selection is always *doing* things. And so we hear about the *mechanism* of selection, as well as the *forces* or *pressures* that operate in it. We learn that natural selection *shapes* the bodies and behaviors of organisms, *builds* specific features, *targets* or *acts on* particular genomic regions, *favors* or *disfavors* (or even *punishes*) various traits or behavioral strategies, *operates* in this way or that, *maintains* DNA sequences, *promotes* adaptation of populations to local environments, *polices* mutations, and, in general, *causes* an endless variety of effects. Darwin himself spoke about how

> natural selection is daily and hourly scrutinising, throughout the world, every variation, even the slightest; rejecting that which is bad, preserving and adding up all that is good; silently and insensibly working, whenever and wherever opportunity offers, at the improvement of each organic being in relation to its organic and inorganic conditions of life (Darwin 1859, p. 84).

This sort of language is all but universal. I think it is safe to say that relatively few references to natural selection by biologists fail to assert or imply that we are looking at something like a humanly contrived *mechanism* with the well-designed power to *do things*, beginning with the activity of *selecting*. This guiding activity is carried out, almost as if by magic, in the sophisticated and almost incomprehensibly well-organized manner necessary to create new forms of the most complex and mysterious entities known to us — living organisms.

If what biologists say has any significant bearing on what they mean, then they are telling us, emphatically, that natural selection is an effective, mechanistic *agent* — an agent of evolutionary change. This is a problem. Developmental systems theorist Susan Oyama was fingering it when she cautioned,

> Nature is not a deciding agent, standing outside organisms and waving them to the right or the left. However much we may speak of selection "operating" on populations, "molding" bodies and minds, when the metaphorical dust has settled, what we are referring to is still the cumulative result of particular life courses negotiated in particular circumstances (Oyama 2000b, p. 81).

Some evolutionists are uncomfortably aware that their use of a phrase intentionally evoking the breeder's "artificial selection" invites mystical belief in a breeder-like agent supervising adaptive evolution. And so they assure us that "natural selection", despite its explicit suggestion of a selecting agent, is "just a metaphor".

The prolifically blogging defender of evolutionary orthodoxy, University of Chicago geneticist Jerry Coyne, spells it out this way: natural selection “is neither a ‘law’ nor a ‘mechanism’.” If we explain the evolution of coat color in polar bears as “‘natural selection acting on coat color’, that’s only our shorthand … There is no external force of nature that ‘acts’ on individuals. There is only differential replication of genes” (Coyne 2010).

In other words, as Coyne goes on to say, the language of agency really refers to a mundane process — “a process that is inevitable”, he adds — and here, as expected, he cites the familiar logic of natural selection.

But it is hard to see this as anything but subterfuge. There is a reason why no effective verbal alternative to the painfully tendentious “selection” has taken hold. The idea of a selecting power is deeply rooted and seemingly ineradicable from the modern biologist’s thinking about evolution. Yes, we can redefine the “metaphorical” selecting agent as a process. But if we then say that the process inevitably yields exactly the results previously ascribed to the intelligent agent — yields what can be viewed as the *policing*, *targeting*, *sculpting*, and *creating* of organisms and their features — we are not getting rid of the agent. We are merely giving it a different name.

When the “variation” Darwin referred to — and by which I put a question mark above — is ignored so far as it results from the organism’s own activity, then it quietly and unobtrusively becomes an implication of the “mechanism” of natural selection. Anything capable of producing the meaningful drama of evolution just *must* possess agential powers. The truth may be that the life in organisms alone possesses such powers, but theorists such as Coyne would rather not come to such a “mystical” conclusion. So they covertly assimilate these powers to the Intelligent Designer called “natural selection”.

It would be well for all evolutionists to acknowledge what I am quite sure even Coyne believes — that nature, in their conception, just happens to work in such a way that it is in fact a kind of agent, accomplishing exactly the kinds of things agents accomplish. Nature is, in Richard Dawkins’ terminology, like a *watchmaker*.

This admission, when made fully explicit, might reasonably lead to a reflection upon the true sources of the imagined evolutionary agency — a reflection beginning with an acknowledgment of the empirically empty nature of the familiar logical formulations of natural selection. And this in turn could prompt a valuable inquiry: where do we see an actual play of agency, as material accomplishment, other than in the lives of organisms? Is there anything beside this accomplishment — this infinitely varied play of well-directed life narratives I have tried to touch upon in the first half of the book — to give empirical substance to evolutionary theory?

But do not underestimate the difficulty of coming around to such fundamental questions. Regarding the “syllogistic core” of natural selection, Gould wrote that “nearly all textbooks and college courses present the ‘bare bones’ of natural selection in this fashion (I have done so in more than 30 years of teaching).” After suggesting that this presentation “does not permit a teacher to go beyond the simplest elucidation of selection as a *genuine force* that can produce adaptive change in a population”, he goes on to say: “In other words, the syllogistic core only guarantees that selection can work … [it] can only rebut charges of hokum or incoherence at the *foundation*” (Gould 2002, p. 126n; emphasis added).

It would be truer to say that the famously simple and compelling logic of natural selection, misconceived as the “foundation” of a powerful theory, has itself become a primary source of hokum in evolutionary thinking. It is a kind of blank template upon which overly credulous biologists and lay people can project their faith. As for the “genuine force” of natural selection that Gould refers to — a supposed causal power over and above those we find actually at play in biological activity — it is a magical invention borne of the refusal to recognize agency in the only place where we ever observe it, which is in the lives of organisms.

This is not to deny that we have learned a great deal — for example, from paleontology and molecular studies — under the banner of “natural selection”. After all, the generality and emptiness of the logical template allows the biologist to impose the required theoretical form upon just about any investigative work. Whatever it is that actually happens, we can always say that the resulting organisms were “selected”. The question is whether the theory adds very much, beyond a certain illusion of explanation.

The inadequacy of the theory of natural selection has long been noticed

It happens that the explanatory vacuity of the logic of natural selection has been recognized by some of the most prominent and reputable evolutionary biologists for more than 150 years. They have been concerned about how complex adaptive innovations are achieved, and how, in general, we can make sense of the evident creativity in evolution. The question that nagged at them can be put this way: What does natural selection *select* — where does selectable variation come from — and why should we think that the mere preservation of already existing variants, rather than the creative production of those variants in the first place, directs evolution along the trajectories we observe?

The influential Dutch botanist and geneticist, Hugo de Vries, framed the matter this way during the first decade of the twentieth century:

> Natural selection is a sieve. It creates nothing, as is so often assumed; it only sifts. It retains only what variability puts into the sieve. Whence the material comes that is put into it, should be kept separate from the theory of its selection. How the struggle for existence sifts is one question; how that which is sifted arose is another (quoted in Gould 2002, p. 428).

It was de Vries who gave currency to the catchy phrasing that has since been repeated many times: “Natural selection may explain the survival of the fittest, but it cannot explain the arrival of the fittest” (de Vries 1906, p. 826). The concern is not easily dismissed. Other biologists have added their own accents, and it is worth pausing a moment to trace a theme that some might see as a kind of subterranean history of evolutionary thought — a history beginning no later than the year after the original publication of *The Origin of Species* in 1859:

“If we take the three attributes of the deity of the Hindoo Triad, the Creator, Brahma, the preserver or sustainer, Vishnu, and the destroyer, Siva, Natural Selection will be a combination of the two last but without the first, or the creative power, we cannot conceive the others having any function” (Sir Charles Lyell [1860], Scottish geologist who laid the crucial uniformitarian foundation for Darwin’s theory).

“It is exceedingly improbable that the nicely adapted machinery of animals should have come into existence without the operation of causes leading directly to that end. The doctrines of ‘selection’ and ‘survival’ plainly do not reach the kernel of evolution, which is, as I have long since pointed out, the question of ‘the origin of the fittest’ … The law by which structures originate is one thing; those by which they are restricted, directed, or destroyed, is another thing” (Edward Drinker Cope [1887, p. 225], noted American paleontologist and formulator of “Cope’s Rule”, which proposed that the organisms of an evolutionary lineage tend to increase in size over time).

“Selection permits the viable to continue and decides that the non-viable shall perish … Selection determines along which branch Evolution shall proceed, but it does not decide what novelties that branch shall bring forth” (William Bateson [1909, p. 96], a founder of the discipline of genetics).

“The function of natural selection is selection and not creation. It has nothing to do with the formation of new variation” (Reginald Punnett [1911], British geneticist who cofounded the *Journal of Genetics*; quoted in Stoltzfus 2006).

“The actual steps by which individuals come to differ from their parents are due to causes other than selection, and in consequence evolution [by natural selection] can only follow certain paths. These paths are determined by factors which we can only very dimly conjecture. Only a thorough-going study of variation will lighten our darkness” (J. B. S. Haldane [1932, pp. 142-43], a major contributor to the twentieth-century consensus theory of evolution).

Regarding specific traits, natural selection “might afford a reason for their preservation, but never provide the cause for their origin” (Adolf Portmann [1967, p. 123], preeminent zoologist of the middle of the twentieth century).

“Natural selection is the editor, rather than the composer, of the genetic message” (Jack King and Thomas Jukes [1969], key developers of the idea of “neutral evolution”).

“In evolution, selection may decide the winner of a given game but development non-randomly defines the players” (Pere Alberch [1980], Spanish naturalist and embryologist, sometimes spoken of as the founder of Evo-Devo — evolutionary developmental biology).

“Natural selection eliminates and maybe maintains, but it doesn’t create” (Lynn Margulis [2011], microbiologist and botanist, pioneer in exploring the role of symbiosis in evolution, and co-developer of the Gaia hypothesis).

Misplaced agency

We began this chapter by listening to Darwin saying that “any being, if it vary however slightly in any manner profitable to itself, under the complex and sometimes varying conditions of life, will have a better chance of surviving, and thus be *naturally selected*”. And we heard much the same from contemporary philosopher, Elliott Sober: “If the organisms in a population differ in their ability to survive and reproduce, and if the characteristics that affect these abilities are transmitted from parents to offspring, then the population will evolve”.

I am not sure why the void at the heart of these statements was so long invisible to nearly all biologists. And, to my dismay, it has likewise taken me far too long to recognize the existence and the significance of this void. How could something so obvious have remained hidden for so long?

In any case, what these statements by Darwin and Sober (and countless other students of evolution) necessarily and unthinkingly start with is living beings themselves, capable of producing variation. Except that the living beings, in the very process of being assumed as the starting point for a compelling bit of logic, drop out of view. They play no role in the elaboration of that logic. Rather, they become “black boxes” from out of which variation just appears. In this way life vanishes from the theory of the evolution of life. It is, once you see it, a startling picture of a theory taken as foundational for all the life sciences.

The blindness we have been subject to has hardly been altered by the repeated glimpses of the truth evidenced in the list of remarks by the authorities above. How else but by virtue of this blindness could we have had the past century’s history of evolutionary science? Indeed, it may well be that most of those authorities only dimly perceived the full implications of their own words. The blindsighted predisposition of the entire discipline of evolutionary biology, along with projection of the organism’s agency onto natural selection, has been too powerful to allow a clean escape to those who have once been habituated to it.

It seems to have been the task of biology over the past couple of centuries to reconceive living things without their life — to see the world of organisms, not through their own eyes, but through ours, which are as if hypnotized by the well-designed automatisms that now shape every dimension of our existence. It is not often that the spell is momentarily broken, as when the philosopher of biology, Denis Walsh — after noting the indisputable yet ignored truth that “organisms are fundamentally purposive entities” — expressed his perplexity by asking, “Why should the phenomenon [of agency] that demarcates the domain of biology be off-limits to biology?”[2]

It is now my intention to discuss evolution by articulating a different point of view, taking life in its own terms. And I see no reason to exclude what we know most directly — and in a higher key, so to speak — through our own existence as organisms. This higher key of consciousness or awareness offers us many possibilities for an immediate, inner understanding of our experience, which is hardly grounds for excluding ourselves, or our understanding of the meanings of life, from a science of organisms.

WHERE ARE WE NOW?

Sweeping Out the Cobwebs Is Good To Do

We can hardly hope to engage profitably the many puzzles and perplexities of evolutionary theory without first “cleaning out the attic of our minds”, where we find stored the heritage of the past century’s theoretical refusal of the life of organisms. I suppose just about everything in this book requires — and is intended to encourage — such a cleaning out in one way or another.

I have, in the above discussion, attempted to show how conventional evolutionary theory has eliminated the organism as the one available source of, or channel for, the kind of adaptive, transformational agency required by evolutionary theory. This ignoring of the organism, together with the prevailing reluctance among evolutionists *explicitly* to acknowledge that they have effectively reassigned the organism’s agency to the “mechanism” of selection, has resulted in a bland formulation of natural selection as if it were the “obvious” operation of an abstract and empty logic. One tries not to speak *openly* of agency at all.

The logic is empty because it refuses to account for the variation that is one of its core presuppositions — refuses to particularize this variation as an expression of the creative life and activity of organisms. But if we do not understand how organisms creatively produce the material of evolutionary change, then we do not understand evolution.

As we will see in later chapters, the advertised logic of natural selection also fails to reckon with the organism’s reliable (and stable!) capacity to produce an inheritance after its own kind. And as we saw in many of the earlier chapters, today’s biology has also failed in understanding the relation between genes and the organism’s fitness — a relation whereby the organism governs its genes much more than its genes can be said to govern the organism.

So the banishing of the organism from evolution occurs in the conceptualization of all three stated requirements for natural selection to occur — variation, inheritance, and differential fitness.

In the next chapter we will look more particularly at the evolutionarily relevant, adaptive, and transformative powers of individual organisms, revealed especially in their development. After that, it will be necessary to look more directly at the evolutionary process itself.

Notes

1. This according to philosopher of biology John Beatty (2010, p. 23), citing correspondence between Darwin and Lyell.

2. Walsh 2015, p. ix. And yet, even Walsh, wonderfully insightful as he is, proceeds to characterize the organism's agency in a strictly materialistic manner, as if it could be understood without accepting at face value the inner dimensions of life. These dimensions include the organism's living (not camera-like or instrument-like — Chapter 24) perception of its surroundings, the evident wisdom at work in its instincts and behaviors, and the intention and volition evidenced in its persistent and well-directed efforts to satisfy its own needs and interests. We are instead given agency without agency, life without life. Such is our way today. Biologists and philosophers call it "naturalizing" agency and purposiveness, as if even our human agency, taken at face value, were decidedly "unnatural". Yet this entire point of view is countered by the decision of those countless worthy individuals who are inspired to exercise their unnatural capacities by dedicating themselves to the tasks of science.

Sources

Alberch, Pere (1980). "Ontogenesis and Morphological Diversification", *American Zoologist* vol. 20, pp. 653-67. doi:10.1093/icb/20.4.653

Bateson, William (1909). "Heredity and Variation in Modern Lights" in *Darwin and Modern Science*, edited by A.C. Seward, pp. 85-101. Cambridge UK: Cambridge University Press. Text available at https://www.gutenberg.org/ebooks/1909

Beatty, John (2010). "Reconsidering the Importance of Chance Variation", in *Evolution: The Extended Thesis*, edited by Massimo Pigliucci and Gerd B. Müller, pp. 21-44. Cambridge MA: MIT Press.

Blackmore, Susan (2014). "A Hundred Walked Out of My Lecture". Available at https://www.richarddawkins.net/2014/08/a-hundred-walked-out-of-my-lecture/

Cope, Edward Drinker (1887). *The Origin of the Fittest: Essays on Evolution*. New York: D. Appleton and Company.

Coyne, Jerry A. (2010). "The Improbability Pump", *The Nation* (April 22). https://www.thenation.com/article/archive/improbability-pump/

Darwin, Charles (1859). *On the Origin of Species*, first edition. London: John Murray. Available at https://archive.org/details/onoriginofspecie00darw_0

Dawkins, Richard (2008). *The Extended Phenotype*, revised edition (1999), reprinted with corrections (2008). Oxford: Oxford University Press. Original edition published in 1982.

Dennett, Daniel C. (1995). *Darwin's Dangerous Idea: Evolution and the Meanings of Life*. New York: Simon and Schuster.

de Vries, Hugo (1906). *Species and Varieties: Their Origin by Mutation*. Lectures delivered at the University of California, edited by Daniel Trembly MacDougal, second edition. Chicago: Open Court. Originally published in 1905. Full text available at https://gutenberg.org/ebooks/7234.

Eldredge, Niles (2000). *The Pattern of Evolution*. New York: W. H. Freeman and Company.

Gould, Stephen Jay (2002). *The Structure of Evolutionary Theory*. Cambridge MA: Harvard University Press.

Haldane, J. B. S. (1932). *The Causes of Evolution*. London: Longmans, Green and Co.

Holdrege, Craig (1999). “What Does It Mean To Be a Sloth?” *NetFuture* #97 (November 3). Latest version is available at https://natureinstitute.org/nature/sloth.pdf

King, Jack Lester and Thomas H. Jukes (1969). “Non-Darwinian Evolution”, *Science* vol. 164, no. 3881 (May 16), pp. 788-98. doi:10.1126/science.164.3881.788

Lenski, Richard E., Charles Ofria, Robert T. Pennock and Christoph Adami (2003). “The Evolutionary Origin of Complex Features”, *Nature* vol. 423 (May 8), pp. 139-44. doi:10.1038/nature01568

Lyell, Sir Charles (1860/1970). *Sir Charles Lyell's Scientific Journals on the Species Question*, edited by Leonard G. Wilson. New Haven CT: Yale University Press. Yale Studies in the History of Science and Medicine, no. 5.

Margulis, Lynn (2011). “Discover Interview: Lynn Margulis Says She's Not Controversial, She's Right”, *Discover* (April). Available online at https://www.discovermagazine.com/the-sciences/discover-interview-lynn-margulis-says-shes-not-controversial-shes-right

Mayr, Ernst (1964). “Introduction”, *On the Origin of Species: A Facsimile of the First Edition*, by Charles Darwin, pp. vii-xxvii. Cambridge MA: Harvard University Press.

O'Neill, Bill (2003). "Digital Organisms", *PLOS Biology*. doi:10.1371/journal.pbio.0000018.

Oyama, Susan (2000a). *The Ontogeny of Information*, 2nd edition, foreword by Richard C. Lewontin. Durham NC: Duke University Press. First edition published in 1985 by Cambridge University Press.

Oyama, Susan (2000b). *Evolution's Eye: A Systems View of the Biology-Culture Divide*. Durham NC: Duke University Press.

Portmann, Adolf (1967). *Animal Forms and Patterns: A Study of the Appearance of Animals*, translated by Hella Czech. New York: Schocken.

Sober, Elliott (1984). *The Nature of Selection: Evolutionary Theory in Philosophical Focus*. Cambridge MA: MIT Press.

Stoltzfus, Arlin (2006a). “Mutationism and the Dual Causation of Evolutionary Change”, *Evolution and Development* vol. 3, no. 3, pp. 304-317. doi:10.1111/j.1525-142X.2006.00101.x

Walsh, Denis (2015). *Organisms, Agency, and Evolution*. Cambridge UK: Cambridge University Press.

Chapter 17

Evolution Writ Small

One might think that the natural place to look for an understanding adequate to the evolutionary history of life would be the powers of self-transformation we observe in the evolving organisms themselves. But it can be dangerous to look in a clear-eyed manner at the creative potentials of living beings. One risks having to acknowledge the evident wisdom and agency so vividly on display. In an era of institutionalized materialism, any suggestion that these inner powers are vital to the entire evolutionary story can only produce the sort of discomfort associated with a taboo.

On the other hand, Stephen Jay Gould ran afoul of no taboo when he effectively ascribed this same wisdom and agency to natural selection. Countering the questions we heard voiced in Chapter 16 about what sort of creative principle could explain the "arrival of the fittest", he asked (referring to several giants of twentieth-century evolutionary biology), "Why was natural selection compared to a composer by Dobzhansky; to a poet by Simpson; to a sculptor by Mayr; and to, of all people, Mr. Shakespeare by Julian Huxley?"

The answer, Gould said, is that the allusions to poetry, musical composition, and sculpture helpfully underscore the "creativity of natural selection":

> The essence of Darwinism lies in its claim that natural selection creates the fit. Variation is ubiquitous and random in direction. It supplies the raw material only. Natural selection directs the course of evolutionary change. It preserves favorable variants and builds fitness gradually.[1]

On its face, this argument for Darwinism was a puzzling one. Its answer to the question how creative variation arises amounted to saying nothing more than "It is everywhere" ("variation is ubiquitous") — which, one might have thought, only added urgency to the need for an explanation. The suggestion seems to be that, because organisms are so expert and prolific at producing new possibilities of life, the evolutionist can simply take their powers of achievement for granted. Because *organisms* so abundantly provide raw materials for creative work, we are somehow free to declare *natural selection* the agent performing this work. It need only preserve all those wonderfully effective new traits.

How easy it is, apparently, to forget that the so-called "raw materials" being preserved are never merely raw materials! At the first appearance of any substantive change, the creative work has already been accomplished — if indeed the change is truly beneficial to a living being. We find ourselves looking, not at random raw materials, but at a viable feature harmoniously incorporated into all the tightly interwoven complexity of life. The only power we know to be capable of such incorporation is that of the organism telling its own story, a story always reflecting the qualitative, dynamic character and developmental potentials of a particular species.

This harmonious incorporation of new features, founded upon whole-cell inheritance and manifested in whole-organism processes of development, is the only place where we see creative evolutionary change originating. The spreading of an already-existing change through a population is not where we see evolutionary novelties arising.

So Gould's response shows us that one of the evolutionist's strategies for coping with taboo agency is immediately to turn the question, "How does creative change arise?" into the different question, "How does creative change, once arisen, spread through a population?" The switch of topics is not hidden, but occurs in plain sight. Only a habit of blindsight relative to the organism's agency seems able to explain such an obvious evasion of a real biological question.

None of this means we need to doubt whatever is true in the idea of natural selection. Selective mortality certainly occurs in one sense or another. Not very organism lives out a full life. But the mere elimination of problematic traits (or defective organisms) through mortality is not the same thing as profoundly transforming the integral unity that every organism is.

The point is not terribly subtle. There is simply nothing in the idea of natural selection that points to the creative capacities necessary for producing new adaptive features — for producing, say, a four-chambered heart (with all its organism-wide implications) from a three-chambered one. There is only the living being whose agency and activity natural selection necessarily assumes and which evolutionists have unconsciously transferred to a mystical "mechanism" of selection somehow operated by the inanimate world.

So, if we do not accept this subterfuge, we are left with the main question for this chapter: What do organisms show us, directly, compellingly, and uncontroversially, about their own powers of organic transformation? Much of the first half of this book contributes to an answer, especially at the physiological and molecular levels of observation. But in the present, evolutionary context, it will be well to look at the organism from a new angle.

A 'magical' power of self-transformation

If I were to tell you that scientists have sequenced the genomes of two entirely distinct organisms — say, a flying creature such as a bird or bat, and a crawling one such as an earthworm or snake — and had found the two genomes to be identical, you would probably think I was joking. Surely such differently structured forms and behaviors could not possibly result from the same genetic instructions! A genome, we've been told time and again, comprises a blueprint for, or otherwise corresponds to, a phenotype — that is, the manifest form and functions of an organism. And what could be more different than the phenotypes of snake and bird?

And yet a good reason for jettisoning the entire notion of "genetic instructions" is that there *are* flying and crawling creatures with the same genetic sequence. A monarch butterfly and its larva, for example. Nor is this kind of thing rare. A swimming, "water-breathing" tadpole and a leaping, air-breathing frog are creatures with the same inherited DNA. Then there is the starfish: its bilaterally symmetric larva swims freely by means of cilia, after which it settles onto the ocean floor and metamorphoses into the familiar form of the adult. This adult, carrying the genome passed on from its larval stage, exhibits an altogether different, radially symmetric (star-like) body plan.

Millions of species consist of such improbably distinct creatures, organized in completely different ways at different stages of their lives, yet carrying around the same genetic inheritance. (See Box 17.1.) This is something to reflect on. How could the transformation possibly be orchestrated, and where lies the power of orchestration?

To speak of the "power of orchestration" will perhaps trigger accusations of "mysticism". And yet the expression of *some* power is right there before our eyes. It is hardly anti-science to let ourselves come up against questions we cannot yet answer. They are what science is for.

One way or another we must come to terms with the fact that the organism and its cells actively *play off* the genomic sequence and all the other available resources within a huge space of profoundly creative possibility. No identifiable physical force compels or directs the cell-by-cell and molecule-by-molecule dissolution and refashioning described in Box 17.1. It is only healthy that such difficulties for our understanding should be acknowledged.

Looking at the pupal case of a fly, the developmental biologist and evolutionary theorist, Wallace Arthur, asked: "What on earth is going on in

Box 17.1

Metamorphosis of an Insect

The goliath beetle (*Goliathus goliatus*), larva and adult.[2]

The British physician and evolutionary scientist, Frank Ryan, described the goliath beetle's metamorphosis this way:

"Rather than a den of repose, we see now that the enclosed chamber of the goliath's pupa really is a crucible tantamount to the mythic pyre of the phoenix, where the organic being is broken down into its primordial elements before being created anew. The immolation is not through flame but a voracious chemical digestion, yet the end result is much the same, with the emergence of the new being, equipped with complex wings, multifaceted compound eyes, and the many other changes necessary for its very different lifestyle and purpose.

"The emerging adult needs an elaborate musculature to drive the wings. These muscles must be created anew since they are unlike any seen in the larva, and they demand a new respiratory system — in effect new lungs — to oxygenate them, with new breathing tubes, or tracheae, to feed their massive oxygen needs. The same high energy needs are supplied by changes in the structure of the heart, with a new nervous supply to drive the adult circulation and a new blood to make that circulation work.

"We only have to consider the dramatic difference between a feeding grub or caterpillar and a flying butterfly or a beetle to grasp that the old mouth is rendered useless and must be replaced with new mouthparts, new salivary glands, new gut, new rectum. New legs must replace the creepy-crawly locomotion of the grub or caterpillar, and all must be clothed in a complex new skin, which in turn will manufacture the tough new external skeleton of the adult. Nowhere is the challenge of the new more demanding than in the nervous system — where a new brain is born. And no change is more practical to the new life-form than the newly constructed genitals essential for the most important new there to turn one animal into another? If we didn't know better, we might venture 'magic' as our best attempt at an answer" (Arthur 2004, p. 45). Arthur's wonder is justified. And he surely expects, as we must, that a more satisfactory answer than "magic" will be forthcoming. Meanwhile, it is worth keeping in mind that the "magical" impression of a phenomenon becomes more powerful in direct proportion to the inadequacy of our current explanatory resources.

role of the adult form — the sexual reproduction of a new generation.

"The overwhelming destruction and reconstruction extends to the very cells that make up the individual tissues, where the larval tissues and organs are broken up and dissolved into an autodigested mush … To all intents and purposes, life has returned to the embryonic state with the constituent cells in an undifferentiated form" (Ryan 2011, pp. 104-5).

Metamorphosis of cells

Frogs and butterflies aside, we are brought up against the same perplexities even when we consider the more "routine" developmental processes in complex organisms. Take, for example, the radical cellular transformations following from a single, fertilized human egg cell. As adults, we incarnate ourselves in trillions of cells, commonly said to exemplify at least 250 major types. And when we count subtypes and transient types, we may well find that — as cell biologists Marc Kirschner and John Gerhart tell us — there are "thousands or tens of thousands of kinds representing different stable expression states of the genome, called forth at different times and places in development" (Kirschner and Gerhart 2005, pp. 179-81).

As researchers hone their ability to investigate single cells, they are finding that even neighboring cells, "identical" in type and occupying the same tissue or niche, reveal great heterogeneity. Every cell is, in whatever degree, "doing its own thing".

Strikingly, however, the cell is not *only* doing its own thing; it is also heeding the "voice" of the surrounding context, which is in turn an expression of the unity of a particular kind of organism. So each cell is disciplined by the needs of its immediate cellular neighborhood as well as those of the entire developing organism, which in turn is conditioned by the larger environment. Every organism — even a single-celled one — is a remarkable diversity within an overall, integral unity.

In humans there are, for example, cells (neurons) that send out extensions of themselves up to a meter or more in length, while being efficient at passing electrical pulses through the body. There are contractile cells that give us our muscle power. There are the crystalline-transparent fiber cells of the lens of the eye; their special proteins must last a lifetime because the nucleus and many other subcellular entities (prerequisites for protein production) are discarded when the fibers reach maturity. There are cells that become hard as bone; as easily replaceable as skin; as permeable as the endothelial cells lining capillaries; and as delicately sensitive as the various hair cells extending into the fluids of the inner ear, where they play a role in our hearing, balance, and spatial orientation.

Many of these cells are as visibly and functionally different, in their own way, as the phenotypes of any two organisms known to us. This, you might think, would interest the evolutionary biologist.

Organisms manage their own germlines expertly

Of all the cellular phenotypes, it would be hard to find one whose differentiation and specialization is more distinctive, or more expertly and intricately contrived, or more purposively managed, than the germ cells of sexually reproducing organisms. We can hardly help acknowledging that parental organisms, in carrying out meiosis, genetic recombination, and mating, play a massive role, not only in preserving and re-purposing the genome, but also in transforming it. Deeply embedded in time like all organisms, and therefore *always facing the future* in every aspect of their being, sexually reproducing animals express their future orientation most immediately and vividly in the gametes whose full “self-realization” belongs to the next generation.

A gamete is at least as specialized as any other cell of the body. At the same time, this gamete, along with the entire lineage leading up to it, must retain the potential to yield the totipotent zygote. That is, despite its commitment to a highly specialized, reproductive function unlike that of any other cell type in the body, the germline cell must at the same time preserve within itself the flexibility and freedom that will be required for its role in producing every cellular lineage of a new organism.

It is an extraordinary mandate, and our bodies must focus extraordinary powers of development upon it. For example, the chromosomes of both sperm and egg will have been modified by epigenetic “marks” (Chapter 7), ensuring that certain genes in the offspring will be active, or repressed, depending on which parent the gene was inherited from. Other widespread marks imposed by the parents will (for the most part) be erased immediately after fertilization. This leaves space for the new organism to structure the spatial, electrical, and chemical characteristics of its chromosomes (and therefore also its gene expression) according to its own developmental potentials.

And, of course, there is the elaborately orchestrated “meiotic ballet” (Page and Hawley 2003) that produces both sperm and egg, each with only half the number of chromosomes found in somatic cells, and with those chromosomes reshuffled and otherwise modified according to a logic and via activities that are still largely beyond any comprehensive understanding.

But one thing is sure: the body’s rearrangement (“recombination”) of its germ-cell chromosomes during meiosis is now showing itself to be highly regulated. Multiple protein complexes and epigenetic modifications of chromosomes function combinatorially, with synergism, antagonism, and redundancy: “The new-found multiplicity, functional redundancy and [evolutionary] conservation" of these regulatory factors "constitute a paradigm shift with broad implications" (Wahls and Davidson 2012).

So we are given no choice but to think of the germline as an expression of that same agency — that same, end-directed transformative power — through which our body subtly, elaborately, and adaptively directs each of its other cell lineages toward a distinctive form and functioning within the unity of the whole. We have seen that this power of transformation comes to expression in the entire cell, quite apart from any mutations in its DNA. And it is just a fact that an entire cell is what each parent passes on as an inheritance to its offspring.

It would be strange indeed if the organism's ability to proceed adaptively and creatively along paths of developmental transformation were to become frozen at the very point where, via the most sophisticated activity imaginable, it prepares its whole-cell bequest for the next generation. Can we reasonably claim that this is the one cell lineage in which the organism's normal, future-oriented activity goes silent? Or that, with all the organism's expertise at producing and stably maintaining diverse phenotypes even without changes in DNA sequence, it "refuses" to employ this expertise when it comes to the preparation of inheritances? Or that the power with which the organism adapts all its cells, tissues, and organs as far as possible to new or unexpected conditions is a power lost to it in the management of its own germline?

If every organism is a living agent, as we all know it to be (whether blindsightedly or otherwise), then surely that agency — whatever its nature, and however conditioned and constrained — is the decisive thing passing between generations. If every organism is an activity, a power of becoming, then the inheritance preparing the way for a new life must first of all be an inheritance of this active power, not of some fixed, already achieved, material result of it. And yet our science has not even addressed the problem of this species-specific formative power, let alone asked what role its unfolding expression — its development of its own potentials — might play in evolution.

Where are we now?

Does the Organism’s Life Have a Bearing on Evolution?

The powerful adaptive plasticity whereby organisms undergo concerted developmental change looks like exactly the sort of change — the only sort of change we know about — that might translate, upon a wider stage, into the diverse organic transformations of evolution. The bare logic of natural selection, after all, makes no reference to the specific potentials concretely realized in the distinctive evolutionary trajectories leading from the simplest cells to redwoods and wildebeest, crayfish and cormorants. On the other hand, we do discover something very like those potentials playing out in the distinctive developmental trajectories leading from a single-celled zygote to osteoblast and endothelium, neuron and neutrophil. And we see them also when we watch the goliath beetle larva (or human embryo) metamorphosing into the adult form.

Only when we ignore the *living powers* required for such transformations can we subconsciously transfer our ineradicable sense of these powers to the working of a blind evolutionary algorithm — something we looked at in Chapter 16.

But the discussion of evolutionary issues and questions in the previous chapter and this one has so far been sketched on far too narrow a canvas. After all, it is not organisms individually that evolve, but populations or species or even larger groups. Furthermore, there is a very real sense in which we cannot even say that a *collection* of organisms evolves. The analogous truth would be this: we cannot say that it is a collection of cells that develops (“evolves”) from a zygote to a human adult. That’s not what we see. Starting with the zygote, and all along the trajectory, it is a whole, an undivided unity, that develops, and the cells come to be and gain their identity by being differentiated out of that unity. They are produced by the developing whole; they do not produce it.

There is no reason not to think similarly about the evolution of a population or species. What prevents us from doing so is our reluctance to recognize biological agency as the interior power of activity it is. But once we do recognize this — once we understand that the agency playing through a developing organism informs and governs perhaps trillions of cells with their relatively independent lives — we have no ground left for thinking it odd that something like this agency must play through a honey bee colony or school of fish or wolf pack or an entire species with countless individual members.

Just as individual cells participate in the life of a complex organism, so, too individual organisms participate in the life of a population, or species. In neither case is it always easy to distinguish what is individual from what is collective. And this suggests that the agency we recognize in individual organisms cannot be cleanly separated from the agency at work in the species — surely an idea the evolutionary theorist might run with.

But these remarks are only a kind of “advance warning” to brace for some (I hope stimulating) intellectual turbulence ahead. Our task now is to keep our eyes open to the reality of organic transformation as we shift our focus from the development of individual organisms to the evolution of populations. We will begin to take up the issues in the next chapter.

Notes

1. Gould 1976. By the time Gould completed his 2002 masterwork, *The Structure of Evolutionary Theory*, he would offer a richly nuanced qualification of these statements. But his fundamental belief in the creative role of natural selection — or, as he would say, its “efficacy” — remained.

2. Goliath beetle larva and adult photo credit: Frantisek Bacovsky.

Sources

Arthur, Wallace (2004). *Biased Embryos and Evolution*. Cambridge UK: Cambridge University Press.

Bateson, Patrick (2017). *Behaviour, Development and Evolution*. Cambridge UK: Open Book Publishers.

Gould, Stephen Jay (1976). “This View of Life: Darwin’s Untimely Burial”, *Natural History* vol. 85, pp. 24-30.

Gould, Stephen Jay (2002). *The Structure of Evolutionary Theory*. Cambridge MA: Harvard University Press.

Kirschner, Marc W. and John C. Gerhart (2005). *The Plausibility of Life: Resolving Darwin’s Dilemma*. New Haven CT: Yale University Press.

Page, Scott L. and R. Scott Hawley (2003). “Chromosome Choreography: The Meiotic Ballet,” *Science* vol. 301 (August 8), pp. 785-89. doi:10.1126/science.1086605

Ryan, Frank (2011). *The Mystery of Metamorphosis: A Scientific Detective Story*. Foreword by Dorion Sagan and Lynn Margulis. White River Junction VT: Chelsea Green Publishing.

Wahls, Wayne P. and Mari K. Davidson (2012). “New Paradigms for Conserved, Multifactorial, *cis*-Acting Regulation of Meiotic Recombination”, *Nucleic Acids Research* vol. 40, no. 20, pp. 9983-89. doi:10.1093/nar/gks761

CHAPTER 18

Teleology and Evolution

To begin this chapter I will briefly consider some of the difficulties evolutionary theorists are likely to have with the idea that purposiveness, intention, and agency play a role in evolution. Then I will assess the nearly universal conviction among biologists that natural selection explains the purposiveness in the lives of organisms as “merely apparent, not real”.

Every organism is continually dying in order to live. Breaking-down activities are prerequisites for building up. Complex molecules are synthesized, only to be degraded later, with their constituents recycled or excreted. In multicellular organisms such as vertebrates, many cells must die so that others may divide, proliferate, and differentiate. Many cancers reflect a failure to counterbalance proliferation with properly directed tearing-down processes.

You and I have distinct fingers and toes thanks to massive cell death during development. The early embryo’s paddle-like hands give way to the more mature form as cells die and the spaces between our digits are “hollowed out”. In general, our various organs are sculpted through cell death as well as cell growth and proliferation. During development the body produces far more neurons than the adult will possess, and an estimated ninety-five percent of the cell population of the immature thymus gland dies off by the time the mature gland is formed.[1]

Despite all this life and death, I doubt anyone would be tempted to describe an embryo’s cells as “red in tooth and claw”. Nor do I think anyone would appeal to “survival of the fittest” or natural selection as a fundamental principle governing what goes on during normal development. *The life and death of cells appears to be governed, rather, by the form of the whole in whose development the cells are participating*.

But this has been a truth hard for biologists to assimilate, since it has no explanation in the usual causal sense. One way to register the problem is to ask yourself what you would think if I suggested that organisms in an evolving population thrive or die off in a manner *governed* by the evolutionary outcome toward which they are headed — that the pattern of thriving and dying off becomes what it is, in some sense, *because* of that outcome. It is not a thought any evolutionist is likely to tolerate.

But perhaps the occasional intrepid researcher will be moved to inquire: “Why not?” After all, we can also ask about the cells populating our bodies: do they thrive or die off in a manner governed, in some sense, by the forthcoming adult form? And here the answer appears to be a self-evident “yes”.

Perhaps, when we have come to accept what we see so clearly in individual development, we will find ourselves asking the “impossible” question about evolutionary trajectories: Does natural selection really drive evolution, or is it rather that the evolving form of a species or population drives what we think of as natural selection? Are some members of an evolving species — just as with the cells of an embryo's hands — bearers of the future, while other members, no longer being fit for the developing form of the species, die out?

What makes this idea seem outrageous is the requirement that inheritances, matings, interactions with predators, and various other factors in a population should somehow be coordinated and constrained along a coherent path of directed change. Unthinkable? But the problem remains: Why — when we see a no less dramatic, life-and-death, future-oriented coordination and constraint occurring within the populations of cells in your and my developing bodies — do we not regard our own development as equally unthinkable?

Few would imagine that our own well-directed development from embryo to adult is owing to an external guiding power or to a conscious "aiming" or planning. Nor need we think that the "developmental path" of evolution is owing to guidance such as an external breeder might supply. Rather, the idea would be that the evolutionary narrative, like the developmental one, arises from the agency and developmental powers playing through cells, organisms, and communities of organisms, as they express their own character and realize their potentials in the presence of the prevailing environmental challenges and opportunities.

So the question is this: once we accept the all-too-evident fact of a coordinating agency at play in a population of cells pursuing a developmental trajectory, do we have any less reason to expect a coordinating agency at play in a population of organisms pursuing an evolutionary trajectory?

Our answer will depend on our willingness to take seriously a plain fact of our experience — a fact stressed throughout the first half of this book: agency and intention, wisdom and meaning, are given expression by organisms in a way that belies our expectations for collected bits of inanimate matter.

It will be part of my contention that a coordinating power at work in evolving populations is as obviously apparent as the analogous power at work in developing organisms. It's not a conclusion based on radical new evidence, but rather one that depends only on a willingness to look with eyes that see, just as we do when observing the processes at work in a developing individual. To witness this coordinating power may not be immediately to understand everything we would like to know about it, but surely our only hope of understanding rests on our first recognizing and acknowledging the observable fact of a directive, purposive activity. My pointing to this observable fact will come in Chapter 19. But first we need to deal with some of the prejudices blocking our way forward.

Are there obvious reasons to reject agency and teleology in evolution?

Every living activity we actually observe is purposive, or "teleological", or, as I have at times called it, "*telos*-realizing". It always has a holistic dimension, and it always represents a further addition to a life story. We find ourselves watching, not necessarily a conscious planning (which humans are capable of), but rather the self-expression, or self-realization, of a living being. Physical events and causes are *coordinated* in the *interests* of a more or less centered *agency* that we recognize in cell, organism, colony, population, species, and perhaps even in ecological contexts.

This coordination, these interests, this agency — they are already assumed, consciously or otherwise, by all biologists in the case of the individual organism's development and behavior. They are assumed, that is (as I have frequently been pointing out), insofar as one is doing biology, and not merely physics and chemistry.

I tried to suggest in the opening section of this chapter that the agency and purposiveness so clearly manifest in the development of individual organisms could just as well manifest itself in evolution. But, to most biologists, this is bound to seem a mere conjecture, and an impossible one at that. Let's listen to a few of the possible misunderstandings that can so easily disturb our thinking about the role of agency — and, indeed, any sort of wisdom or intention (or, more broadly, interiority) — in evolution.

"How can you jump so casually from the hypothesized agency of a single, developing individual to that of vast, co-evolving populations?"

When we speak, not about physical processes as such, but rather about an underlying biological agency, intention, and purposiveness, then the distinction between an individual animal as a collection of molecules, cells, and tissues, on the one hand, and an entire population as a collection of organisms, on the other, becomes an open question.

The whole business of *telos*-directed biological activity, wherever we have observed it, is to bridge radically different physical processes. That is, it brings diverse and complex physical phenomena — for example, in the brain, heart, liver, intestines, and skin of a developing mammal — into integral unity and harmony, making a larger whole of them. When we have seen this purposive coordination and harmonization in one context involving many distinct animate elements, it is only natural to look for it in other, higher- or lower-level contexts also involving distinct animate elements.

The coordinating agency we are talking about *establishes* the relatedness of physical entities (whose constituents may be continually changing) and does not *arise from* them. The problem biologists have at this point lies in their pre-existing insistence that all aspects of our understanding of life must be couched solely in terms of lawful physical interactions. But this doesn't work against the claim that the rational, thoughtful, purposive, and intentional dimensions of what is going on — that is, the most fully meaningful dimensions — are almost by definition not physical, but yet are very real. The biologist may want to quarrel with this view, but the quarrel cannot be furthered by endlessly repeating that the meaning of things shouldn't be mentioned because only physical interactions are allowed into the discussion.

The fact is, we do not currently understand the nature and origin of the observed powers of coordination in living organisms, just as we do not understand the nature and origin of physical law. Nor can we assume that the inanimate principles are more fundamental than the animate ones. What we *can* assume is that the teleological dimension of an organism's performance comes into play at the very root of its material being, just as does the play of physical law. If anything, an inherent power to orchestrate physically lawful activity in a purposive manner, however poorly understood, would seem higher or more fundamental than the physical processes being orchestrated.[2]

Given our ignorance of the ultimate nature of things, the most immediate path forward when the teleological question arises in a particular context, is simply to observe whether the adjustment of means toward the fulfillment of needs and interests is actually occurring in that context.

But this much can be said already. Wherever we find *telos*-realizing entities somehow bound together in a larger unity, we see one example after another where the more comprehensive entity or context manifests in turn a teleological character of its own. Whether it is all the molecules in a cell, or all the cells in an organism, or all the organisms in a coherent group (say, an insect colony or mammalian social group), we always find a weaving of lower-level narratives into the distinctive fabric of a larger story.

So we can hardly help asking the teleological question in an evolutionary context: When a species moves along its own coherent evolutionary trajectory, is it not displaying its own sort of *telos*-directed developmental potentials? And then we must be willing to look with open and honest eyes.

“You speak of a harmonization of physical elements in tune with meaning and purpose. But how can physical processes be harmonized without relevant causal connections between them? We can see such connections clearly in a developing organism. But huge numbers of different organisms in radically different species, often scattered over a large geographic area, are a different matter.”

Yes, a very different matter. And certainly any purposive coordination of physical events does require causal connections between them. Those connections are precisely what must be coordinated. But the members of evolving populations of organisms have no fewer or less relevant causal connections than the aggregated cells in an individual. Eating and being eaten are surely causal! And, of course, not only predator-prey relations, but also mating choices, territorial movements, learning experiences, lateral gene transfer mediated by microorganisms and viruses, and many other causal interactions already figure importantly in conventional evolutionary theory.

Isn't the entire body of evolutionary theory today concerned with physical causation? Surely conventional theory is a *physical theory* and gives us all the relevant causal interactions we need. The question about purpose, intention, and meaning is a question about the organization and coordination of the physically transformative processes already identified by evolutionary biologists.

Moreover, when considering causal interactions among evolving organisms, we shouldn't forget the special role of cognition. We can hardly help acknowledging the highly intentional causal connections between all those organisms possessing specialized sense organs. And today we know that specialized senses exist even at the level of single-celled organisms, who display a sophisticated agency at both the individual and collective levels.

When speaking of "sensing", we always refer to something more than "being impinged upon by external forces". We refer to a perception of that which has *meaning* for the cell or organism, and this is linked to a meaningful response by the organism. If there were no detectable, purposive response to a particular feature of the environment, we would have no way to know that perception had occurred.[3]

Actually, the reality of a coordinating power weaving through and governing large, scattered populations of organisms is already put on display for us before we even think about evolution. It is displayed, for example, in instinctual behavior such as that of migrating monarch butterflies in eastern North America. Huge numbers of these gather from throughout a wide area, including parts of the United States and Canada, and travel thousands of miles over multiple generations to a precise spot in Mexico — all this along aerial pathways they have never traveled before.

Or consider the sophisticated collective behavior of a wolf pack, an ant colony, or even the cells — bacterial and otherwise — of a biofilm. The latter has been termed a "city for microbes", and the complex, teleologically rich organization of a city is not an unapt picture of the life of a biofilm. In all these different sorts of collectives, the power of end-directed coordination, whatever we take it to be, seems to work across the relevant communities, and all the way down to the molecules that actively participate in the performance of the various organisms.

So I come back to my initial line of thought. Suppose, for the sake of argument, that an animal's mating choices and its preparation of inheritances for its offspring are guided, or end-directed, in a manner leading to coherent evolutionary change. How would this be more problematic for our physical understanding than all the cellular inheritances within the many proliferating and radically diverging cell lineages in a complex, developing organism? These, too, are guided in a manner leading to coherent developmental change — that is, leading toward the integral, overall unity of the mature organism.

Surely an individual organism no more "knows", in anything like a human sense, about the evolutionary trajectory it is caught up in than an individual cell "knows" about the developmental trajectory it is caught up in. It cannot know the character and needs of the larger process. But in both cases the individual entity does in fact lend itself to participation in the larger process. It lends itself to the agency working through the more encompassing whole of which it is a part.

Yes, the particular principles of coordination in evolution must in some ways differ from those in individual development, as we will see shortly. In fact, they will not be the same in any two, distinct contexts. But whatever the principles are, we will not discover them by looking at the laws of physics and chemistry. We will begin to grasp them only when we are able to read each particular context in terms of its own meanings, self-realizing powers, and directions of movement. We are already pretty good at this in the case of individual development. There is no reason not to try looking in an analogous way at evolving populations.

It only needs adding that while an effective evolutionary agency might be required to coordinate physical processes, it would not itself be what we usually think of as a physical power. There is no reason, for example, to doubt that it might in some ways work in widely separated, physically non-interacting populations. The existence of species-wide instincts is suggestive in this regard.

“It sounds as though the myriad forms of your wonderful ‘agency’ can accomplish just about anything. The different agencies of individual organisms can somehow blend together so as to become the *telos* of a species or larger group, just as the *telos* of the larger group can fragment into subunits — all in order to vitalize and give identity to everything from the smallest bacterium to the entire biosphere as a single whole. Do you have any idea how all this *works*?”

I pointed out above that we no more understand the nature and origin of the observed power of coordination in living organisms than we do the nature and origin of physical law. But I would add: just as, through observation, the physicist can learn about the *working* of ideal (immaterial) laws and forces, so the biologist can learn about the *working* of the teleological activity of living beings. In general, biologists do not have a particularly difficult time of it (even if they are blindsighted about their own understanding). Nor does any pet owner or observer of nature.

It is true that, in the organism (and in all biology), diverse processes are coordinated toward a common end. And it is also true that this is understandable only because a principle of interpenetration is universal in biology. The general rule is that we always find ourselves looking at wholes embedded within still larger wholes, and contexts overlapping other contexts. This is clearly evident when we consider the integrated unity of a physical body with all its cells, tissues, and organs. It may take some effort, but we have to learn to think in terms of this embeddedness of wholes and overlapping of contexts.

In Chapter 6 we heard how the botanist Agnes Arber described the relative character of organic wholes:

> The biological explanation of a phenomenon is the discovery of its own intrinsic place in a nexus of relations, extending indefinitely in all directions. To explain it is to see it simultaneously in its full individuality (as a whole in itself), and in its subordinate position (as one element in a larger whole) (Arber 1985, p. 59).

From flocks, herds, and schools, to bee and ant colonies, to parasitic and symbiotic pairs, to more or less closely aggregated communities of cells, to the highly differentiated and elaborately integrated cells of our own bodies — there are many different contexts of agency. The one thing we can know directly is that we discover agency and intention wherever we find participants bound together in a larger, more or less focal community that unfolds its activity along a continuous and well-directed pathway according to its own distinctive meanings.

The honey bee hive functions, in this sense, as a (relative) whole with its own agency. We have no difficulty recognizing this agency in the hive's pattern of coherently directed activity. The participants in the hive have no absolute discreteness or wholly independent identity. But neither do they lose all individual identity. It is a matter of one identity participating in a greater one.

If, as Arber suggests, biology presents us with interpenetrating wholes, then we should also expect to see interpenetrating agencies expressed in those wholes. The distinctive character of, say, a mammalian genus (or any other taxonomic group) is not silenced by, but rather informs, the character of each species within the group.

"Isn't the idea of agency, when applied to organisms in general, a rather disastrous anthropomorphism?"

Anthropomorphism is indeed a supreme danger in biology. Think, for example, of all the human activity we rather blindly import into the organism when we analogize it to a machine. (See the section about the machine model of organisms in Chapter 10.) Similarly, it would be highly misleading to think of biological agency as if it were like the directive activity of a sovereign and individual human agent.

To begin with, human agency itself is not as neat and unambiguous as we may be inclined to suppose. A fully sovereign individual does not exist. Who among us can say that he is motivated solely by his own will? Who does not at times yield gladly to internalized and inspiring "voices" — for example, of teachers and mentors, or religious figures, or uplifting texts. And who does not also wrestle with lower, less worthy urges? What young child subjected to extreme abuse does not carry into adulthood the burden and unfreedom of a psychic complex expressing some of the disastrous ideational, affective, and volitional powers of his abusers? Or again, which of us is absolutely immune to the collective ecstasy, hysteria, or rage of a massive crowd "rooting for the home team" or submitting to the spell of a charismatic leader?

It is true that, when we speak of agency, we speak of capacities we ourselves routinely and, at times, consciously exercise. But we must also admit that our experience of our own agency is closely bounded on all sides by mystery. We do not fully understand where our thoughts and actions come from, or how our intentions move our bodies. It would be a mistake to clothe the mystery of biological agency in the imagined form of a grandly sovereign, all-knowing human individual.

And if we cannot be entirely clear about the sources of agency in our own lives, we can hardly be dogmatic about the nature of the agency — or diverse agencies — at work in a single bee colony, a particular species of rodent, or the biosphere as a whole.

But nothing prevents us from being good observers of living beings, which is also to be observers of the clear *manifestations* of biological agency. In this way we become familiar with the complex and perhaps many-voiced character — the way of being — of particular organisms. We learn to know "from the inside" one species as distinct from another. And we can try our best to bring the same disciplined observation to bear on ecological settings, communities of organisms, or the entire historical panorama of evolution.

We do not need to understand the "ultimate nature" of agency in order to describe its immediate manifestations. This is a truth familiar to us, for we have no difficulty describing with more or less insight the character of a friend, even though we do not know the ultimate nature of the human being.

"But the simple fact is that evolution is not individual development. Don't you need to reckon with this fact?"

Yes. As I remarked above, the principles of coordination in one context must differ in one degree or another from those of a different context. They are what make each context what it is.

One obvious difference between development and evolution is that cycles of individual development are endlessly and reliably repeated, so that no one can avoid at least unconsciously recognizing their teleological character. Time and again, amid all the inconstancies of life and environment, mouse zygotes develop into adult mice.

Evolution, by contrast, encompasses the totality of life on earth, and occurs only once. No more than in reading a good novel can we predict, mid-way through the story, its later outcome, even if that outcome turns out to be the end toward which everything was tending.[4] This non-repeatability of evolution makes it all too easy, for those bent on doing so, to "forget" everything they know about the creative and end-directed character of all the life processes through which evolution occurs.

There are, of course, other distinctions between individual and evolutionary development. In the latter case we see (in those organisms reproducing sexually) a continual merging of separate hereditary lineages. There is also the fact of hybridization across species, genera, and even families. None of this commonly occurs among the cells of a developing organism. And some evolutionary features figuring strongly in current theorizing — symbioses of various sorts, cultural inheritance, and lateral gene transfer — also serve to remind us that, while communities of organisms can be vitally important even for individual development, they become central in evolution.

We have no reason to assume that the play of purposiveness across all the cells of a complex, developing organism is exactly analogous to its play among the members of a species or population. Nor need we asume that the more or less fixed stages through which individual development passes give us a neat roadmap for the course of evolution.

We do, however, have at least one foundational principle: whether we are focused on genes or traits, *nothing can become a fact of evolution that was not first a fact of individual development*. The very substance of evolutionary transformation must first of all reveal itself within individual organisms.

The current unwillingness of biologists to reckon with the possibility that evolution gives us a coherent, *telos*-realizing narrative does not appear to be explained by the differences between individual development and evolution (which are very real), but rather by a refusal to take seriously the problem of active biological wisdom and agency in either case.

The uncomfortable truth is that biology has yet to come to terms with the physically puzzling fact of purposive biological activity — which is to say, *all* biological activity. To suggest that evolution is *telos*-realizing is not to suggest some new kind of problem. It is merely to say: let's face up to the reality of teleological development and behavior that has already long been staring us in the face.

The shortest path to confusion is circular

But haven't I been committing an egregious sin of omission? Surely any reader with a conventional biological training will think so. After all, doesn't everyone know that evolution by natural selection "naturalizes", or explains away, the agency and purposiveness we observe in organisms? That is, explains it without appeal to any principles other than purely physical ones?

Biologists often think of purposiveness, or teleology, under the concept of function, as when they say that a trait is "for the sake of" this or that, or an organ exists "in order to" achieve a particular end. And so, as philosopher David Buller has summarized common usage, "the function of the heart is to pump blood, the function of the kidneys is to filter metabolic wastes from the blood, the function of the thymus is to manufacture lymphocytes, the function of cryptic coloration (as in chameleons) is to provide protection against predators".

But all this poses difficulties for a science that would honor its materialist commitments, since the concept of function, as Buller observes, "does not appear to be *wholly* explicable in terms of ordinary causation familiar from the physical sciences". Whereas kidneys may continually adjust their activities and their own structure *in order to* do the best possible job of filtering metabolic wastes from the blood, no physicist would say that falling objects adjust their activities and their own structure *in order to* reach, as best they can, the center of the earth. More generally, organisms may strive to live, but physical objects do not strive to maintain their own existence. Organisms, so it seems, have intentions of their own, whereas physical objects are simply moved from without according to universal law.

So the problem for biologists has been to explain, or explain away, their persistent and seemingly inescapable language of purpose. And the need is to do so in a respectable, materialistic manner — that is, to explain it without having to acknowledge that organisms really are purposive beings in the sense of exercising, or being possessed by, an interior (immaterial) activity of a thought-full and intentional sort. But this problem — so we are told — has been fully solved in recent decades.

Buller, who was writing at the turn of the twenty-first century, was able to point to a "common core of agreement" representing "as great a consensus as has been achieved in philosophy" — an agreement that "the biological concept of function is to be analyzed in terms of the theory of evolution by natural selection". More particularly, "there is consensus that the theory of evolution by natural selection can provide an analysis of the teleological concept of function strictly in terms of processes involving only efficient causation" — the kind of "purposeless" causation physical scientists accept as applicable to the inanimate world (Buller 1999).

So we no longer need to think of organisms as having genuine intentions, purposes, or *telos*-realizing drives of their own — no longer need to struggle with the problem of teleology, or end-directed activity. Teleology, we must believe, has been tamed, leaving biologists safe in a world without interiority or living thought.

To put the most common version of the idea very simply (and not many working biologists seem worried about the need for a more sophisticated formulation), organisms are said to possess teleological, or purposive, features *because those features are present by virtue of natural selection*. That is, they were selected for the very reason that they effectively serve the organism's crucial ends of survival and reproduction. And since natural selection is supposed to be a perfectly natural process — meaning that it involves nothing "mystical" like *real* purpose, intention, or thought — we can know that the functionally effective traits given us by natural selection are straightforward exemplars of physical lawfulness and nothing else, whatever they might *look* like.

If this feels as though it is cheating a bit, then you might want to trust your intuition — for more than one reason. I will briefly touch the issue from two different angles.

(1) The problem of the "arrival of the fittest" remains

To say that natural selection preserves traits promoting the survival of organisms does nothing to explain how the teleological character of those traits might be compatible with materialist thought. This depends on what the preserved traits are and how they arose. The preservation of an already existing trait is an entirely different matter from its nature and origin. Claiming that teleological features or activities already existed at some time in the past and then were preserved by natural selection merely pushes the problem of "naturalizing" them — making them acceptable solely in physical and materialist terms — back to an earlier time, without solving it.

We heard about this in Chapter 16, where prominent figures in evolutionary biology over the past century and more complained that natural selection — even if it explains the survival of the fittest — cannot explain the arrival of the fittest. In conventional evolutionary thought the arrival of traits is simply assumed, with natural selection then playing a role in their preservation and their spread throughout a population. Yes, purposive features — *if* they could be had in a strictly physical world — would conduce to the survival of organisms, and therefore might be preserved. But how does this bare fact make these features, in Buller's words, "explicable in terms of ordinary [physical] causation”? If we felt that a trait needed to be “naturalized”, how would its coming into existence (and then being proven beneficial by natural selection) demonstrate its naturalization?

Given the historical persistence of the complaint by leading biologists about natural selection and the arrival of the fittest, it is remarkable that the arguments today about how natural selection explains teleology generally proceed without so much as an acknowledgment of the problem.

(2) The explanation assumes what it is supposed to explain

It is important to realize that purposiveness is not just a particular, late-arriving trait, but runs through *all* biological activity. It is reflected in the coordinating principles that account for the integral, interwoven unity of the organism’s life. The complexity theorist and philosopher of biology, Peter Corning — who appears to hold a conventional, materialist view of life — was nevertheless gesturing toward this purposive unity when he wrote that living systems “must actively seek to survive and reproduce over time, and this existential problem requires that they must also be goal directed in an immediate, proximate sense … Every feature of a given organism can be viewed in terms of its relationship (for better or worse) to this fundamental, in-built, inescapable problem” (Corning 2019).

Rather than being just one more discrete trait that might have been neatly evolved at some particular point in evolution, the *telos*-realizing capacity of organisms reflects their fundamental nature. It is what “living” means. We are always looking at a live performance — a future-directed performance, improvised in the moment in the light of present conditions and ongoing needs — not a mere “rolling forward” of some blind physical mechanism set in motion eons previously.

Here we encounter a staggeringly obvious problem. You will recall from Chapter 16 that natural selection is supposed to occur when three conditions are met: there is variation among organisms; particular variations are to a sufficient degree inherited by offspring; and there is a “struggle for survival” that puts the existing variants to the test. But — and this is the crucial point — *all* the endlessly elaborate means for the production of variation, the assembly and transmission of inheritances, and the struggle for survival just *are* the well-regulated, end-directed activities whose teleological character biologists have tried to explain away. So the basic conditions enabling natural selection to occur could hardly be more thoroughly teleological.

In other words, the purposive performance of an organism is a pre-condition for anything that looks at all alive and capable of being caught up in evolutionary processes of trait selection. So the common form of the argument that natural selection explains the apparent purposiveness of all biological activity appears to assume the very thing it is supposed to explain. Purposiveness is built into the core presuppositions of natural selection itself, which therefore presents us with the problem instead of removing it. It would be truer to say that teleology explains natural selection than that selection explains teleology.

Although this problem regarding the explanation of teleology has been almost universally ignored among biologists, it has not been entirely overlooked. Georg Toepfer, a philosopher of biology at the Leibniz Center for Cultural Research in Berlin, has stated the matter with perfect directness:

> With the acceptance of evolutionary theory, one popular strategy for accommodating teleological reasoning was to explain it by reference to selection in the past: functions were reconstructed as 'selected effects'. But the theory of evolution obviously presupposes the existence of organisms as organized and regulated, i.e. functional systems. Therefore, evolutionary theory cannot provide the foundation for teleology.[5]

An aversion to meaning

The theory of natural selection gives us no argument explaining away the self-evident purposiveness of organisms. To the contrary, it confirms the theorist's largely unacknowledged recognition of this purposiveness. For we can make sense of natural selection only after we have thoroughly internalized, from childhood on, a vivid awareness of the lively agency, whether of cats and dogs, birds and squirrels, worms and fish, or of the animals in our laboratories. The scientist can take this agency for granted without having to mention or describe it, since everyone else also takes it for granted.

This may be an extraordinarily naïve way to do science and philosophy, but, well, there it is. And so one speaks ever so casually of individual "development", or the "struggle for life", or the "production of variation", or "reproduction and inheritance" — all in order silently to import into theory the full range of the living powers that made biology a distinct science in the first place, but that few today are willing to acknowledge explicitly in their theorizing.

In this way, amid contradiction, circular reasoning, and what I have called the biologist's "blindsight", the materialist preserves his preferred picture of a meaningless existence. All he needs to do is appeal to natural selection, that "universal acid" (Dennett 1995) capable of dissolving all objections to what one wants to believe.

The result is clear. Several decades ago the British biologists Gerry Webster and Brian Goodwin had already noticed that "the organism as a real entity, existing in its own right, has virtually no place in contemporary biological theory" (Webster and Goodwin 1982). Goodwin later elaborated the point in his book, *How the Leopard Changed Its Spots*:

> A striking paradox that has emerged from Darwin's way of approaching biological questions is that organisms, which he took to be primary examples of living nature, have faded away to the point where they no longer exist as fundamental and irreducible units of life. Organisms have been replaced by genes and their products as the basic elements of biological reality (Goodwin 1994, p. vii).

The banishing of organisms from evolutionary theory was also an obscuring of biological purposiveness. It may even be that the banishing happened mainly *for the sake of* this obscuring. Yet who can doubt that, if we ever do take the purposive organism into account at anything like face value, the results could be of explosive significance for all of evolutionary theory?

It is difficult to pinpoint whatever lies behind the extraordinary animus the biological community as a whole holds, not only toward teleology, but indeed toward any meaningful dimension of life or the world. But the animus seems as deeply rooted as it could possibly be. Michael Ruse, who might be regarded as a dean of contemporary philosophers of biology, once briefly referred to an article by the highly respected chemist and philosopher, Michael Polanyi, in this manner:

> Polanyi speaks approvingly, almost lovingly, of “an integrative power … which guides the growth of embryonic fragments to form the morphological features to which they embryologically belong.”

And what was Ruse’s response?

> One suspects, indeed fears, that for all their sweet reasonableness the Polanyis of this world are cryptovitalists at heart, with the consequent deep antipathy to seeing organisms as being as essentially physico-chemical as anything else … Shades of entelechies here! (Ruse 1979)

The assumption that the Polanyis of this world are antipathetic toward the idea that organisms are “as essentially physico-chemical as anything else” is a mere distraction from the real issue. No one needs to, or should, deny that organisms are perfectly reliable and unexceptionable in their physical and chemical nature. (Certainly Polanyi does not deny this.) By injecting his unfounded “suspicions” into his argument, Ruse simply abandons his responsibility as a philosopher.

The real question has to do with the distinctive organizing ideas we find to be characteristic of organisms. After all, no one claims that the lawful ideas of the physicist are mystical just because they are not physical things. They belong to the nature of inanimate phenomena. So why should we refuse to acknowledge the readily observable organizing ideas characteristic of animate phenomena? There is a burden of explanation here that Ruse seems not even to recognize, let alone to engage.

The real antipathy appears to be on Ruse’s part. One wonders exactly what violation of observable truth he saw in Polanyi’s reference to “an integrative power” that “guides” embryological growth. No biologist would dare deny that embryological development is *somehow* integrated and guided toward a mature state. And it is difficult to understand how any actual integrating and guiding could be less than the expression of an effective “power”, however we might end up understanding that term. Just think how much less justification there is for all the conventional references to the “power”, “force”, and “guidance” of natural selection! (On that, see Chapter 16.)

As for Ruse’s shuddering at the term “entelechy” (sometimes rendered as “soul”), the scholar who is perhaps the foremost interpreter of Aristotle today translates the Greek *entelecheia* as “being-at-work-staying-itself” (Sachs 1995, p. 245). What better characterization of an organism and its distinctiveness relative to inanimate objects could there possibly be? Every biologist who uses the conventional term “homeostasis” (a system’s maintenance of its own material stability) or, better, “homeorhesis” (a system’s maintenance of its characteristic activity) is already saying something similar to “being-at-work-staying-itself”. It’s the way of being of any organism. The Aristotelian term is useful for reminding us that an organism is first of all an activity, and its activity is that of a centered agency possessing a remarkable coordinating and integrative power in the service of its own life and interests.

On our part, we will now do our best to read the organism and its activity back into evolutionary theory. In doing so, we will ignore the strange taboo against accepting living powers and purposiveness as relevant to the theory.

WHERE ARE WE NOW?

Is Teleology Disallowed in the Theory of Evolution?

An animal’s development from zygote to maturity is a classic picture of *telos*-realizing activity. Through its agency and purposiveness, an animal holds its disparate parts in an effective unity, making a single, ever more fully realized whole of them. This purposiveness informs the parts “downward” from the whole and “outward” from the inner intention, and is invisible to strictly physical analysis of the interaction of one part with another.

Biologists in general have failed to take seriously the reality of the animal’s agency, and have considered it unthinkable that something analogous to this agency could play through populations of organisms in evolution, just as it plays through populations of cells in an organism. I have tried to suggest that there are no grounds for making a radical distinction between the two cases.

And then, addressing the idea that natural selection explains (or explains away) biological purposiveness, I focused on two closely related problems:

- The *preservation* of purposive (functional) traits — or any traits at all — by natural selection neither explains their *origin* nor shows how they can be understood solely in terms of physical lawfulness.

- Selection itself is defined in terms of, and thoroughly depends on, the purposive lives of organisms. This purposiveness must come to intense expression in order to provide the basic pre-conditions for natural selection. These conditions are the production of variation; the assembly and transmission of an inheritance; and the struggle for survival. Since the entire logic of natural selection is rooted in a play of purposiveness, it cannot explain that purposiveness.

My aim has been to clear away some of the major stumbling blocks biologists inevitably feel whenever evolution is said to have a purposive, or teleological, character. There remains the question whether evolution does *in fact* show such a character. Does the evolution of species show the same kind of creative thought we see at work in the development of individual organisms? Can we even intelligently imagine such thought *not* being at work?

We will see that — just as with individual development — the question is answered as soon as it is asked. In both cases, once the metaphysical biases against the very idea of teleology are removed, all we need to do is look, and it's as if our eyes themselves are enough to give us our answer.

Notes

1. Rich, Watson and Wyllie 1999. The authors go on to mention that, while researchers naturally tend to focus on cell survivors, "it is striking that, even with a sophisticated understanding of survival signals, we still know remarkably little of the reciprocal process by which, of the seven million germ cells present in the ovary of the mid-term human foetus, the vast majority is lost by the time of birth".

2. This orchestration of physical processes occurs, as I said, at the root of their material being, which is very different from the human engineer's arrangement of material parts "from the outside". I discuss the machine model of organisms in Chapter 10.

3. In a play of meaning (as in a poem, novel, or any worthy *line of thought*) we always find a coherent *movement toward* — toward an end, or completion, or a greater fullness of the expression of a present context. So, too, every organism is continually bringing its own distinctive life story toward fuller realization in accordance with the meaning of its own context. Every sensing and responding becomes an integral "utterance" within that same story.

4. Actually, the same unpredictability is true of individual development. If we were watching a developmental sequence for the first time, we would not be able to predict its mature outcome based on what we saw half way through. And yet we would recognize retrospectively that this outcome was the end toward which everything was tending all along.

5. Toepfer 2012. There is also this from University of Toronto philosopher of biology, Denis Walsh. Natural selection, he says, occurs

> because individuals are capable of mounting adaptive responses to perturbations. This capacity to adapt allows individuals to survive in unpredictable environments and to reproduce with startling fidelity, despite the presence of mutations. It is adaptation which explains the distinctive features of natural selection in the organic realm and not the other way round. (Walsh 2000).

Therefore, he adds, "the programme of reductive teleology cannot be successfully carried out". Then there is the following succinctly stated criticism by the independent philosopher, James Barham:

> Selection theory does nothing to help us understand what it is about functions that makes it appropriate to speak of their "advantage", "benefit", "utility", etc. for their bearers. Natural selection is like a conveyor belt which transmits a biological trait or function from one generation to the next … But natural selection cannot explain how the capacity of biological functions for success or failure arose out of physics in the first place, for the simple reason

> that the selection process has no hand in constituting biological traits as functions (Barham 2000).

Given my limited familiarity with the literature, I would not be surprised if there exist a few similar criticisms along the same line, at least among philosophers. But my own experience suggests that finding them amid all the conventional evolutionary thinking requires some serious digging.

Sources

Arber, Agnes (1985). *The Mind and the Eye: A Study of the Biologist's Standpoint*, with an introduction by P. R. Bell. Originally published in 1954. Cambridge UK: Cambridge University Press.

Barham, James (2000a). "Biofunctional Realism and the Problem of Teleology", *Evolution and Cognition* vol. 6, no. 1.

Buller, David J. (1999a). "Natural Teleology", introduction to *Function, Selection, and Design*, edited by David J. Buller. Albany NY: SUNY Press, pp. 1-27.

Bridges, B. A. (1969). "Mechanisms of Radiation Mutagenesis in Cellular and Subcellular Systems", *Annual Review of Nuclear Science* vol. 19, pp. 139-78. doi:10.1146/annurev.ns.19.120169.001035

Cook, Norman D. (1977). "The Case for Reverse Translation", *Journal of Theoretical Biology* vol. 64, no. 1 (January 7), pp. 113-35. doi:10.1016/0022-5193(77)90116-3

Corning, Peter A. (2019). "Teleonomy and the Proximate–Ultimate Distinction Revisited", *Biological Journal of the Linnean Society*, vol. 127, no. 4 (August), pp. 912-16. doi:10.1093/biolinnean/blz087

Crick, Francis H. (1958). "On Protein Synthesis", Symposia of the Society for Experimental Biology no. 12: *The Biological Replication of Macromolecules*, pp. 138-63.

Crick, Francis (1970). "Central Dogma of Molecular Biology", *Nature* vol. 227 (August 8), pp. 561-63. doi.org/10.1038/227561a0

Dennett, Daniel C. (1995). *Darwin's Dangerous Idea: Evolution and the Meanings of Life*. New York: Simon and Schuster.

Elespuru, R. K. and K. Sankaranarayanan (2006). "New Approaches to Assessing the Effects of Mutagenic Agents on the Integrity of the Human Genome", *Mutation Research* vol. 616, pp. 83-89. doi:10.1016/j.mrfmmm.2006.11.015

Goodwin, Brian (1994). *How the Leopard Changed Its Spots: The Evolution of Complexity*. New York: Charles Scribner's Sons.

Jacob, François (1977a). "Evolution and Tinkering", *Science* vol. 196, no. 4295 (June 10), pp. 1161-66. doi:10.1126/science.860134

Langer, Susanne K. (1967). *Mind: An Essay on Human Feeling* vol. 1. Baltimore MD: Johns Hopkins University Press.

Pinker, Steven (1997). *How the Mind Works*. New York: W. W. Norton and Company.

Rich, Tina, Christine J. Watson and Andrew Wyllie (1999). "Apoptosis: The Germs of Death", *Nature Cell Biology* vol. 1 (July), pp. E69-71. doi:10.1038/11038

Ruse, Michael (1979). "Philosophy of Biology Today: No Grounds for Complacency", *Philosophia* vol. 8, (October), pp. 785–96. doi:10.1007/BF02379065

Sachs, Joe (1995). *Aristotle's Physics: A Guided Study*. New Brunswick NJ: Rutgers University Press.

Shapiro, James A. (2011). *Evolution: A View from the 21st Century*. Upper Saddle River NJ: FT Press Science.

Toepfer, Georg (2012). “Teleology and Its Constitutive Role for Biology as the Science of Organized Systems in Nature”, *Studies in History and Philosophy of Biological and Biomedical Sciences* vol. 43, pp. 113-19. doi:10.1016/j.shpsc.2011.05.010

Walsh, Denis (2000). “Chasing Shadows: Natural Selection and Adaptation”, *Studies in History and Philosophy of Science, Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* vol. 31, no. 1 (March), pp. 135-53. doi:10.1016/S1369-8486(99)00041-2

Webster, Gerry and Brian C. Goodwin (1982). “The Origin of Species: A Structuralist Approach”, *Journal of Social and Biological Structures* vol. 5, pp. 15-47. doi:10.1016/S0140-1750(82)91390-2

CHAPTER 19

Development Writ Large

We have found throughout the preceding chapters that all biological activity, including at the molecular level, is thoroughly and irreducibly directive. Some biologists explicitly acknowledge the fact, and all biologists implicitly recognize it in their choice of descriptive language (see Chapter 2).

This leads naturally to the central conclusion of this book — a conclusion I will develop in this chapter — which is that *we already know more than enough to say that evolution is a purposive, or directive, or* telos*-realizing, process*. I understand that you may have difficulty coming to terms with this conclusion. But, as I hope to show, it is really just a matter of admitting to ourselves what we in fact know quite well. After all, an implicit recognition of the directiveness of living activity, however repressed, is the only thing that lends to the mass of biological description and theory any appearance of plausibility. Organisms just are beings that accomplish things, and those accomplishments are what biology is about.

The essence of this “unacknowledged knowledge” lies in the striking truth that living activities are quite unlike inanimate processes. Whether consciously or unconsciously, every organism directs its actions toward the future. At least, *we* experience the meaning and the time dimension of their actions that way. We can readily assume that most organisms themselves have no *experience* of aiming toward the future. But — and this is a crucial observation too easily ignored in evolutionary theorizing — there is a clear sense in which the objective character of their activity does exhibit what we cannot help seeing as a future-oriented meaning and directionality.

I try to clarify some of the issues surrounding all this in the book’s final chapter. But it has been both explicit and implicit throughout all the chapters that organisms are purposive beings, and the purposes are carried out with an incomprehensible wisdom and facility. A cell replicating its DNA, proceeding through division, and intricately coordinating its ever-changing patterns of gene expression; higher animals mating and providing for their young; a zygote undergoing all the “miraculous” transformations of embryonic development — these activities are, in terms of the prevailing principles of biological explanation, all but out of reach. Processes we conventionally accept as “causal” do not explain a developing organism’s living narrative — its ceaseless adjustment and coordination of causal activity so as to move directively toward a characteristic future that is not yet there.

But such *telos*-realizing narratives are also so “boringly” familiar that we cannot help taking them for granted. We assume their decisive role in every biological context we look at, and cannot “un-know” them even when we are theorizing from a position that ignores or denies them. And so we have the two sides of biology today: an uneasy, theoretical disregard of what seems ungraspable or dangerously mysterious, and a carefree, unexamined taking-for-granted of the powers so obviously at work in those all-too-familiar mysteries.

My aim in this chapter — an aim grounded in all the preceding chapters — is to facilitate the changed angle of vision that can enable the reader to grant full recognition to what is already known. I want to jog evolutionary thinking out of its customary pathways.

Evolution as a transformation of developmental processes

No one will dispute that a wolf's development, proceeding from a fertilized egg cell through embryonic and fetal stages to the pup's birth, and then on through maturation to adulthood, is highly directive. It is an improvisationally coordinated, inherently meaningful, and adaptive movement embodying past results while oriented toward the future. It is part of an ever more complete self-expression. We would never say of a geyser or planet that it is, in this sense, moving toward fuller self-expression.

Yes, the organism's development is a path full of unpredictable variation, never exactly repeated in different wolves. But this makes it all the more impressive that the entire trajectory remains persistently wolf-like despite all the adjustments to disturbances and despite all the adaptations to changing conditions — and also, despite the wolf's feeding day after day on the flesh of other animals, which it never fails to convert into its own flesh. The individual wolf, embedded within its physical and social environment, exhibits the organizing power of its species, and is capable of negotiating a wolf-like path through the exigencies of life.

The three-week-old heart of the embryonic wolf is dramatically different from that of the six-week-old heart, which in turn differs from the heart immediately following birth (at about nine weeks), and this again differs from the heart of the mature wolf. It is presumably uncontroversial to say that any biologist who studies wolf physiology and development (something you can be assured I have never done myself) will expect the processes leading from one stage to another to show all the features of organic activity. Everything will prove thoroughly directive (*telos*-realizing), plastic, and adaptive, with earlier features serving as an effective preparation for later ones. Causation will be inescapably holistic, so that context-dependence will be a theme in all physiological, morphological, and behavioral explanation.

I doubt whether anyone would want to suggest that there are ways to get from the embryonic heart to the mature heart via any pathway *not* directive in the sense of all development.

But suppose we look at an evolutionary sequence, such as the classic textbook lineage of the horse. How might we imagine that a heart, structured *that way* fifty million years ago in the fox-sized horse ancestor, *Hyracotherium*, becomes this heart, structured *this way* in the Triple Crown winner, American Pharoah?

Can we realistically picture this evolutionary metamorphosis being achieved by processes fundamentally less well coordinated, less seamless and integral, or less consistent with the general character of all living activity, than the developmental transformations bridging the differences between, say, a two-month- and five-month-old horse embryo? Is there any fundamental difference in the nature of the developmental transformation achieved in the two cases? Is there any basis whatever for us to assume that the change of the heart at two stages of an evolutionary lineage is somehow less organically complex and less directive in character than the change in the heart at two stages of a single organism's development?[1]

It is, after all, the whole nature of a developmental narrative to proceed directionally and seamlessly *from here to there*. It would require a powerful and unexpected set of arguments to show that nature, employing any conceivable set of historical processes, could effectively transform such a developmental narrative otherwise than by entering into and respecting the terms governing all such narratives. The need is to improvise as necessary while managing a frightfully complex, systematic, re-organizing, future-oriented activity that is the only basis for developmental transformation we have ever witnessed in organisms.

American Pharoah is as remarkable an endpoint for the evolutionary trajectory from *Hyracotherium* as it is for the developmental trajectory from its own zygotic stage. If we can hardly help taking for granted the directive activity required for the latter sort of development, can we find any justification for overlooking the necessity for directive activity in the former sort?

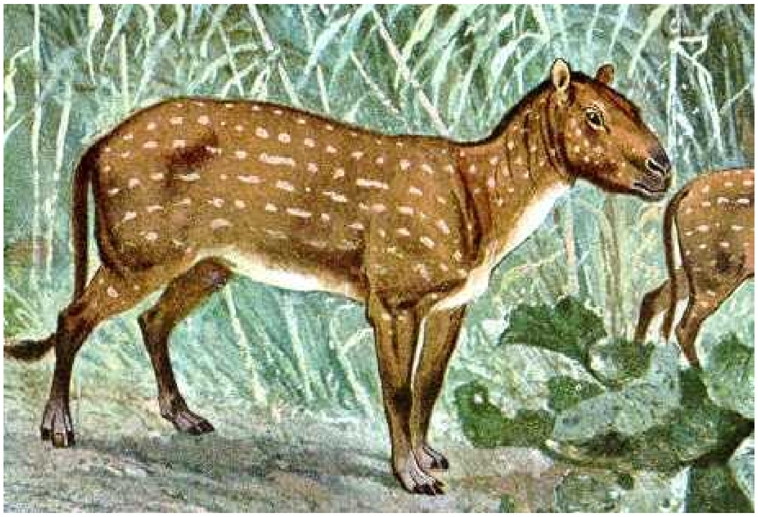

Figure 19.1. An artist's conception of the fox-sized horse ancestor, *Hyracotherium* (*Eohippus*).[2]

Figure 19.2. Triple Crown winner, American Pharoah.[3]

A thought experiment

Let’s assume that horse-racing enthusiasts never stop breeding horses. We’ll assume further that, having magically transported ourselves into the future, we are holding in our hands the exhaustive, generation-by-generation, molecular-level and phenotypic documentation for a thousand-year evolutionary lineage running from the 2015 Triple Crown winner, American Pharoah, to the greatest mega-champion of all time. Call him Chinese Ceasar if you wish.

It is a safe bet that Chinese Ceasar differs significantly from American Pharoah. The specific differences will depend, among other things, on the qualities that breeders valued throughout those thousand years — running speed presumably being one of them. Due to the principle of holism, through which a change in one feature of an organism is linked to change in many others, it is hard to imagine what sort of horse we would be looking at a thousand years from now. But surely it would be a horse of a different color.

Surely also, this would be a case of *directed* evolution — “directed”, not merely in the sense of “channeled in part by environmental and developmental constraints”, but also “resulting from intentional agency”. After all, the entire line of descent would have been intended by breeders and their ideals. But *would we recognize this fact if we were unaware of the breeders’ role?* That is, could we discover, solely from the horse lineage itself, the fact that it progressively realized certain ideas, or guiding principles, or intentions?

The question seems to me important. Strongly held opinion has it that actual evolutionary history shows no directive or progressive aspect — not, at least, in an intentional sense bearing much resemblance to the directionality imposed by breeders. But if the answer to our question is, “No, we wouldn’t necessarily be able to recognize Chinese Ceasar as the result of directive evolution” — if, in fact, we have not yet learned to distinguish the features of a directive evolutionary lineage from those of a non-directive one — then on what grounds can anyone claim that normal evolution is not directive?

If I am not mistaken, then, here is a fair request we can make of evolutionary theorists. Show us how we might distinguish, at least in principle and in the metamorphosing organisms themselves, a non-directive evolutionary process from a directive one. Or, if they cannot do this, let them explain the evidence upon which they conclude that evolution is, in general, nondirectve.

Figure 19.3. A museum skeleton of *Hyracotherium*.[4]

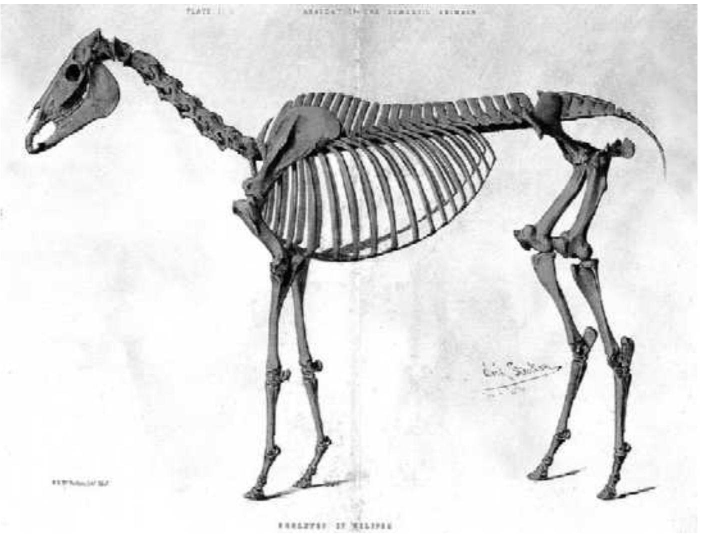

Figure 19.4. Skeleton of a modern horse. The two images are not shown at the same scale. The horse skeleton is several times larger than the ancestral skeleton.[5]

Experiment concluded?

As it happens, a year or so after I first wrote the preceding section, I discovered that philosopher Daniel Dennett had already pursued the same thought experiment — and had received an answer. He pictured aliens visiting earth and tampering with natural selection for a while, then departing. He asked: “Would their handiwork be detectable by any imaginable analysis by biologists today?”

Dennett did the sensible thing: he consulted some biologists. “All the biologists I have queried on this point have agreed with me that there are no sure marks of natural, as opposed to artificial, selection” (Dennett 1995, pp. 316-19).

This is a dramatic acknowledgment, although the real significance of it seems to have escaped Dennett. He was clearly thinking of intelligent design when writing this passage, and feared that ID advocates might seize on the idea that you can’t disprove the intervention of an external Designer in evolutionary history. So he was quick to reply that, barring discovery of a feature positively *requiring* a Designer’s intervention — a feature that natural selection without a Designer could not explain — there was no refutation of Darwinism to be had here.

If you want a measure of how thoroughly the organism has dropped out of sight in today’s evolutionary theory, Dennett’s account offers it. Apparently it did not even occur to him to ask, not about an intelligent Designer, but about organisms themselves, whose powers of directive development, physiology, and behavior, displayed right before our eyes, constitute their entire life story. The question, still ignored today, is how the organism’s living activity participates, *out of its own purposive, cognitive, and intentional nature*, in the broader intentional coherence displayed so clearly in evolving populations.

To be as unambiguous as possible: the question here is not about an external designer, but about a purposiveness inherent in populations of organisms analogous to the purposiveness we see playing through the many more or less independent cells within an individual body. And the question is hardly out of bounds, given biologists' apparent agreement that "there are no sure marks of natural, as opposed to artificial, selection". One wonders how it is that the idea of meaningfully directive evolution has been so scorned if in fact all biological processes we can directly observe are irreducibly directive, and if we have no ready means for distinguishing a non-directive evolution from a directive evolution — or even from an *artificially* directive evolution.

You might think that the point could be reversed. We could ask, "How can anyone scorn the idea of non-directive evolution if in fact we have no ready means for distinguishing non-directive from directive evolution?"

But it is part of my present argument that there is good reason why we cannot point to a distinction between the two forms of evolution. It is impossible to imagine in any coherent fashion an evolutionary-developmental process that is not subject to the guiding principles or ideas inherent in the form progressively being realized. So the only thing biologists are ever in fact thinking of is directive evolution, whether they have acknowledged it to themselves or not.

The wisely purposive lives of organisms — their striving for life and survival, the intricate wonders of their capacity to reproduce, their masterful ability to gather and organize a unified, workable inheritance for their offspring — these "miracles" of directive activity (in terms of which, as we have seen, natural selection is defined) are so thoroughly imprinted upon our experience that not even an entrenched scientific materialism can dislodge them as implicit assumptions of our evolutionary theorizing.

So it is not that we have a choice between directive and non-directive evolution. The only biological activity we ever see or can consistently imagine at any scale is directive activity.

The potential shapes and functions of proteins are virtually infinite. So a major question in evolutionary studies has been, "How, amid this vast landscape of possibility, can more or less random mutations in DNA lead, in any reasonable amount of time, to the particular proteins useful for an organism's current adaptive needs?" This question has been a flashpoint for debate between intelligent design advocates and conventional biologists. The debate is, to say the least, perplexing. That's because the foundational assumption on both sides — that *natural* biological processes are inherently non-directive — is so dreadfully wrong.

It is, in the primary sense, populations that evolve, not individual organisms

The relevant fact is that *nothing* in an organism escapes being caught up in meaningful and directive processes. There is simply no available context for talk of "random" mutations. The processes of DNA maintenance, replication, damage repair, and mutational change are among the most fully characterized and the most intricately purposive and directive activities we have so far explored at the molecular level. DNA damage repair and the closely related incorporation of mutational change are, perhaps, orders of magnitude more complex than the spliceosomal activity we looked at in Chapter 8. It takes place in the same fluid environment as RNA splicing. And there is the same play of organizing *ideas* and ideal *reasons* for what goes on — reasons of a sort that cannot be derived from concepts of physical lawfulness.

At this point — without ever addressing the decisive problem of the rational coherence of molecular activity in the cell — evolutionary theorists are quick to tell us that, although genetic mutations are in general nonrandom, they are nevertheless crucially random in one regard:

> Mutations are claimed to be random in respect to their effect on the fitness of the organism carrying them. That is, any given mutation is expected to occur with the same frequency under conditions in which this mutation confers an advantage on the organism carrying it, as under conditions in which this mutation confers no advantage or is deleterious (Graur 2008).

So then another debate arises: “Are mutations really random relative to their benefit for the organism, or are they ‘directed’?” This is where the question of purposiveness or direction in evolution is thought to come to a sharp focus. The effort to prove or disprove the existence of “directed mutations” is often pursued as if it would tell us about the directiveness of evolution.

The question about mutations in the individual organism is certainly significant and worth pursuing. But here, too, the underlying assumption of most debate makes little sense. If we are talking about a *telos*-realizing evolutionary process, then the question is not about a mutation’s benefit for the individual organism, but rather about its relation to whatever is being realized in the overall evolutionary process. We are not helped much in this by making assumptions about the relation between mutations and individual fitness. Rather, we must investigate how the individual organism is *caught up* in, and *participates* in, directive processes involving populations, species, and even larger groupings.

This is much the same as with individual development. We recognize the meaningful path of development, not merely by looking at what happens to an individual cell, but by picturing the coordinated activity of all the cells in the body. Any individual cell, or group of cells, may, as we saw in the introduction to Chapter 18, be caught up in a coordinated dying-off process essential to the formation, say, of a particular organ. It is not, primarily, the welfare or fate of individual cells we are interested in, but the larger developmental transformation. Or: we are interested in the individual cell because of the way it participates in, and is informed by, that larger movement.

But the evolutionary parallel here requires some explanation.

Far from a simple, linear process

We know that individual development is marked by more or less dramatic periods of especially rapid, intense transformation. In our own development, profound changes occur around the time when the young child is taking its first steps and speaking its first words. Likewise with puberty and menopause. Then, too, there is the entire, nine-month period of human embryological development, from the zygote onward. This pre-natal phase is marked by vastly more physiological and morphological change than occurs throughout all the subsequent decades of life.

Perhaps even more dramatic are the many millions of species — for example, among insects and amphibians — that undergo one or another kind of metamorphosis. A worm becomes a butterfly, a tadpole transforms into a frog. This reorganization can be both swift and virtually total. (See the description of insect metamorphosis in Chapter 17.) But such times of emphatic change typically occur between extended periods of relative stasis, or slower change.

That a similar pattern often, but not always, holds in evolution was argued in 1972 by paleontologists Niles Eldredge and Stephen Jay Gould, who called the pattern “punctuated equilibrium”. Since then various forms of the idea have been broadly accepted, so that another prominent paleontologist, Robert Carroll, could write of vertebrate evolution that “instead of new families, orders, and classes evolving from one another over long periods of time, most had attained their most distinctive characteristics when they first appeared in the fossil record and have retained this basic pattern for the remainder of their duration” (Carroll 1997, p. 167).

It’s not just the relative suddenness of change that matters in the present context. More significant is the remarkably nonlinear character of the processes by which major evolutionary innovations occur. My colleague, the whole-organism biologist Craig Holdrege (to whom I am deeply indebted for many of the insights in this section),[6] has drawn attention to one of the central lessons emerging from paleontological work: when something dramatically new arises in the fossil record, it is typically foreshadowed by fragmentary “premonitions” (not his word) in various taxonomic groups, some of which may then go extinct. There is no smooth, continuous, single line of development leading to the new form, which may arise not only rather suddenly, but also as a novel synthesis and transformation of the earlier, scattered, premonitory gestures.

Holdrege shows this very clearly in his book chapter on the frog (“Do Frogs Come from Tadpoles?”).[7] After mentioning that no frog fossils have come to light from before the Jurassic period of the Mesozoic era, he notes that “the first frog fossils have virtually the same proportions and the same skeletal morphology as today’s frogs”. Earlier, there were indeed rare transitional forms possessing some frog features, especially features of the head. These were “a far cry from frogs, but if you know frog morphology well, you can see hints of what is to come”. He goes on to say of the paleontological record that

> the hints or foreshadowing of what will come later are not manifest in only one type of fossil, but in several. Various elements of what appears later in the new group are manifest in earlier periods, but in different lineages. Evolutionary scientists often speak in this connection of “mosaic” evolution, since various characteristics appear in different arrangements in different organisms … Even when a trove of fossils is available, such as in

> the horse family (Equidae), it is not the case that they line up in a neat series. Rather, there is surprising diversity in the forms that predate modern horses (Holdrege 2021, p. 249).

In some of his other work Holdrege has pointed to the same reality in the human and pre-human fossil record. Using accurate models or professional drawings of the available skulls, done to scale, he asks students to arrange them in an order showing an apparent progressive movement toward the human form. It can be an informative (if frustrating) exercise, since no definitive sequence emerges. One skull may show a seemingly more "advanced" feature than the other skulls, while at the same time showing more "primitive" ones (Holdrege 2017).

All this resonates with other facts that have been in the news these past few years — news bearing on the most recent human evolution. We have heard a good deal about cross-breeding between humans, Neanderthals, and Denisovans, and also about the prevalence of variation within populations. The genomes of a major part of the present human race contain a significant proportion of Neanderthal and/or Denisovan DNA, and these elements are thought to play significant roles in human biology.

Figure 19.5. A cichlid fish (*Pundamilia [Haplochromis] nyererei*), one of hundreds of cichlid species in the lake region of eastern Africa.[8]

Then, too, there is the broader fact that *hybridization* between species and genera — and even between families — is now linked to rapid evolutionary change. One impressive story was reported in the journal *Science*, in an article titled "Hybrids Spawned Lake Victoria's Rich Fish Diversity". Among cichlid fish in Africa's Lake Victoria, the rate and extraordinary extent of diversification has, we're told, "baffled biologists for decades". A mere 15,000 years ago there were only a few ancestral species, whereas today — as a result of a remarkable "adaptive radiation" — 500 or so species exist. Some of them "nibble plants; others feed on invertebrates; big ones feast on other fish; lake bottom lovers consume detritus". Varying in length from a few centimeters to about 30 centimeters, they "come in an array of shapes, colors, and patterns; and dwell in different parts of the lake".

The report goes on:

> Now, researchers have evidence that ancient dallying between species from two watersheds led to very genetically diverse hybrids that could adapt in many ways to a new life in this lake. Increasing evidence has shown that hybridization, once considered detrimental, can boost a species's evolutionary potential. Suspecting that might be the case in these fish, researchers sequenced hundreds of cichlid genomes, built family trees, and compared the genomes of fish throughout that part of Africa. They discovered that parts of cichlid genomes have been mixed and matched in different ways through time, with various

> descendants being repeatedly separated and reunited as lakes and rivers dry up and refill. These hybrids had extensive genetic diversity that fueled rapid speciation (Pennisi 2018).

And even more radical than hybridization has been the dramatic, *endosymbiotic* origin of different life forms at the cellular level. This has yielded some of the most decisive evolutionary transitions of all time. For example, the presence of chloroplasts (in plant cells), mitochondria (in animal cells), and perhaps a number of other cellular organelles, including possibly the eukaryotic cell nucleus — are now thought to have resulted from the merger of very different life forms. That is, a once free-living, single-celled organism becomes permanently internalized as a functioning part of a different (host) single-celled organism.

It took a long time for biologists to accept theories of endosymbiosis, which were first put forward more than a hundred years ago. This is hardly surprising because of the seemingly insuperable nature of the problem: once joined together, the two cells, with their entirely different life cycles, would have to proceed harmoniously through all the necessary and diverse functions of the new, united entity, including cell division. So it seemed that a successful merger of two very different organisms would have required an almost unthinkable and well-directed sort of “management” by both the host organism, and the internalized one. But the truth appears to be that, at critical moments in evolutionary history, such powers were indeed exercised.

Still further, we should not forget the broad fact of *horizontal gene transfer* — that is, the movement of genetic material laterally between different kinds of organisms rather than vertically through inheritance from biological parents. This movement is often mediated by bacteria or other microorganisms, and can involve the transmission of genes between widely differing organisms. Where this gene mixing occurs — and it is known to have occurred extensively, especially in simpler life forms — it throws a wrench into all theorizing about slow, linear, evolutionary change based on random mutations passed down from parent to offspring.

As if that were not enough, we have to reckon with the major role viruses have played in shaping many genomes, including those of mammals. For example, every human genome is thought to contain several times as much DNA of viral origin than the DNA of all the protein-coding genes combined.

Then again, there is the entire mass of microorganisms comprising the *microbiomes* of humans and other organisms. The collective genetic content of the human microbiome rivals that of our own genomes in total mass, while also being functionally crucial for our lives.

A sprawling narrative

So you get the picture. Traditional questions about "directed mutations", their effect upon the evolutionary "fitness" of individual organisms, and their spread through a single population via "normal" genetic inheritance — these have been rendered less relevant by our growing knowledge of actual evolutionary processes. We need to raise our sight to the larger collective sphere in which profound and relatively rapid evolutionary change can occur — the sphere where we can discover the kind of unexpected synthesis of diverse and scattered potentials described above.

Within this larger sphere, one thing we can truthfully say about mutations (or the creation of genetic variation) is that they can be healthy for the species. They provide resilience in the face of changing environments. This is true regardless of any "fitness or evolutionary benefit" for the individual. And it is, of course, the species as a whole, not just the individual organism, that is evolving. But not *only* the species. There are (as we have seen) diverse interactions of many sorts among different groups of organisms, resulting in the movement of both genetic and non-genetic material between individuals, populations, species, and higher-level groups.

And so we arrive at an extraordinarily complex picture. A "strange dalliance", a few Neanderthal genes here and Denisovan genes there, the hidden and genetically seething world of microorganisms and symbionts constituting a vital part of the substance of higher organisms, the wholesale, lateral exchange of genetic resources among lower organisms, the thriving of some lineages and the extinction of others that nevertheless carried for a time part of the essential "mosaic" of evolutionary potentials, and, finally, the relatively sudden convergence, or synthesis (evolutionary metamorphosis), of all those potentials in a new evolutionary configuration — well, if you want to ask about the directiveness of evolution, then all this, along with the overarching agency so clearly recognizable both in the outcome and in the only conceivable path of coordination for getting there, is the relevant stuff of your question. We are not looking at the isolated matter of a mutation's fitness for an individual organism.

One thing is certain: we see no lack of room for a play of intentional, coordinating activity in evolution, just as we see a play of developmental intention through all the cells of, say, a mammal's body. And in both cases it is the *result* of the activity, together with the necessarily coordinated, adaptive *nature* of the entire process for getting there, that tells us a directive and purposive activity has been going on.

Our current ability actually to *trace* this directive activity in evolution may be rather poor, if only because the fossil record tells us so little about the sprawling evolutionary interactions we know must have occurred. But we do know that the development of the individual horse, American Pharoah, required all the familiar, directive powers we have observed in developmental biology generally, all the intricate coordination, adaptation, and compensatory adjustment to disturbances, all the evident wisdom, thoughtfulness, and well-directed intention.

And we also know that much *more* than the wisdom of individual development was required for the evolutionary transformation of *Hyracotherium* into American Pharoah. For not only was it necessary for every ancestral animal in the relevant lineages to be capable of undergoing its own development, but so, too, the relations between mates and between predators and prey, together with all the other “complications” hinted at above, had to come under a directive, coordinating agency capable of realizing all the various metamorphoses of interacting lineages along the way.

All this is decisive to acknowledge in a forthright spirit. However much we may not yet understand, we see the *fact* of this kind of directive evolutionary metamorphosis in the picture already given to us.

Where are we now?

Evolution As a Form of Development

We have been led by all the preceding chapters to this present one, in which we have concluded that the question of the directiveness of evolution turns out to be almost trivially simple, with an unproblematic answer: evolutionary “development” must be at least as directive as the development and life processes of an individual organism.

Their ignoring of the fundamental reality of directiveness in the life of organisms is a central reason why biologists have, for decades, denied all possibility of a coherent *telos*-realizing aspect of evolution. This emphatic denial has taken hold despite their inability consistently to imagine a non-directive form of evolution, and despite their admission that they have no criteria for distinguishing a directive from a non-directive form.

The fact is that no one can avoid assuming the organism’s thorough-going directiveness, because it is just too obvious. And that inescapable assumption, whether or not acknowledged, is why it is impossible to imagine a non-directive form of evolution distinct from a directive one. The effort would be like trying to imagine an evolution of stones. The intention to formulate such a view of evolution is always undercut by one’s awareness of the actual nature of organisms, as revealed in the development, physiology, and behavior of animals.

We have also seen in this chapter that the coordinating agency at work in evolution cannot be centered in the individual organism, but must play through complex interactions among many organisms and populations. We have noted a distinctly nonlinear aspect of much of evolution, where foreshadowings of changes to come (“glimpses of the future”) can be found scattered through diverse lineages, leading, at certain critical points, to a more or less dramatic and sudden reconfiguration and synthesis of much that had gone before. This reconfiguration can involve hybridization, lateral gene transfer, and symbioses, among other things, in addition to the predatorial, mating, and migratory activities that have long figured centrally in evolutionary theorizing.

All this means that the relation between a mutation and the individual fitness of an organism is no more central to the origin of species than the “fitness” of an individual cell is central to the development of a complex organism’s adult form. In fact, the death of many cells may at some point constitute their positive contribution to the adult form. Similarly, the coordinated patterns of life and death within evolving populations can be recognized as essential to evolution.

In general, we have seen that the directive processes of evolution present us with no fundamental problems of purposiveness and agency that have not already been presented to us by the directive processes of development. Purposiveness and agency are definitive givens of biology, and their denial destroys biology as an independent science of life.

But while this chapter, building on the preceding ones, sets forth my positive argument for acknowledging the essential directiveness of evolutionary processes, the discussion nevertheless remains incomplete. We have yet to look at the way whole organisms and whole-organism inheritance have been effectively negated or rendered invisible by the almost universal preoccupation with genes at the foundation of evolutionary theory. We take this up, along with questions about inheritance and about the “disreputable” topic of holism, in our next three chapters.

Notes

1. The most obvious difference between individual development and evolutionary development is that coordination in the latter case must play, not through the countless cells in a single organism, but rather the countless individuals in various populations. We considered this difference in Chapter 18. But see also below on the nature of evolutionary transformation.

2. Figure 19.1 credit: Anonymous (CC BY-SA 4.0).

3. Figure 19.2 credit: Coolmore photo.

4. Figure 19.3 credit: Ghedoghedo (CC BY-SA 3.0).

5. Figure 19.4 credit: Wellcome Images (CC BY-SA 4.0).

6. I also owe a good deal of my understanding of evolution in general to the writings and lectures of Holdrege, as well as to personal conversations with him. See especially his chapters on the giraffe and the frog in *Seeing the Animal Whole — And Why It Matters* (2021).

7. Holdrege 2021, pp. 213-56. Holdrege’s answer to the question, “Do frogs come from tadpoles?” is, in a very important sense, “no”. The appearance of the frog represents the achievement of something new, not the mere “rolling forward” of fully determinative “mechanisms” already present in the tadpole. Upon seeing a tadpole for the first time, we could not predict the existence of the forthcoming frog, as if it were a physical necessity.

8. Figure 19.5 credit: Kevin Bauman (CC BY-1.0).

Sources

Dennett, Daniel C. (1995). *Darwin's Dangerous Idea: Evolution and the Meanings of Life*. New York: Simon and Schuster.

Graur, Dan (2008). "Single-Base Mutation", Wiley Online Library, *eLS*. doi:10.1002/9780470015902.a0005093.pub2

Carroll, Robert L. (1997). *Patterns and Processes of Vertebrate Evolution*. Cambridge UK: Cambridge University Press.

Pennisi, Elizabeth (2018). "Hybrids Spawned Lake Victoria's Rich Fish Diversity", *Science* vol. 361, no. 6402 (August 10), p. 539. https://science.sciencemag.org/content/361/6402/539

Holdrege, Craig (2017). *Diversity in Human Fossil History — A Teaching Unit on Hominid Evolution*. https://www.natureinstitute.org/book/craig-holdrege/diversity-in-human-fossil-history/about

Holdrege, Craig (2021). *Seeing the Animal Whole — And Why It Matters*. Great Barrington MA: Lindisfarne.

Mayr, Ernst (1961a). "Cause and Effect in Biology", *Science* vol. 134, no. 3489 (November 10), pp. 1501-6. Available at https://www.jstor.org/stable/1707986

Popov, Igor (2008). "Orthogenesis Versus Darwinism: The Russian Case", *Revue d'histoire des sciences* vol. 61, no. 2, pp. 367-97. https://www.cairn.info/revue-d-histoire-des-sciences-2008-2-page-367.htm

CHAPTER 20

Inheritance and the Whole Organism

In 1923 Wilhelm Johannsen, the Danish plant physiologist and pioneering geneticist who had earlier given biologists the word “gene”, expressed concern about the way genes were being conceived as neat, cleanly separable causal units. He made the following curious remark, which remains today as intriguing as ever, despite its never having prompted much serious discussion within the field of genetics as a whole:

> Personally I believe in a great central ‘something’ as yet not divisible into separate factors. The pomace-flies in Morgan’s splendid experiments continue to be pomace flies even if they lose all “good” genes necessary for a normal fly-life, or if they be possessed with all the “bad” genes, detrimental to the welfare of this little friend of the geneticists (Johannsen 1923, p. 137).

The pomace-fly, of course, was the fruit fly (*Drosophila melanogaster*) that Thomas Hunt Morgan, in his Princeton University laboratory, was famously converting into a “model organism” for genetic studies. Thanks to procedures for mutating genes, controlling the mating of the flies, and tracing the inheritance of traits, this was the fateful period during which “genetic” was becoming synonymous with “heritable”. The fact that whole cells — and not merely genes — pass between generations was progressively losing its significance in the minds of biologists interested in inheritance and evolution. They could, after all, now *see* cause and effect displayed in the relation between mutated segments of chromosomes and changes in eye color or defective body parts.

Johannsen realized that this new genetic work was based on the assumed existence of separate and independent causes of traits, and therefore left untouched what might easily be seen as the central problem of inheritance: the faithful reproduction of kind, or type — that is, the maintenance of the integral unity that harmonizes all the particular traits and parts of an organism and expresses that organism’s characteristic way of being. While mutated genes might result in (typically pathological) *differences* in certain narrowly conceived traits, this sort of change never reached through to the fundamental identity of the organism. Whatever the introduced variations (mutations), the pomace-flies always remained pomace-flies.

Johannsen’s problem arises because we can hardly help recognizing the distinctive unity of a living being — a unity we have difficulty equating to any particular parts. Rather, the organism seems in some way *responsible* for its parts. We never see an organism being constructed or assembled from already-existing parts. In its development it works to bring them about — to differentiate them out of a prior unity. Every organism is the power to do this work, and the power is not derivable from its results. If some of its parts become deformed, the organism works out of its unity to compensate for the deformities, doing so according to the way of being of its own kind.

But what sort of genetically investigated *differences* was Johannsen dismissing as disconnected from the problem of the whole? In his brilliant, and still decisively relevant[1] 1930 book, *The Interpretation of Development and Heredity*, the British marine biologist E. S. Russell took up Johannsen's concern. "When we say that a child shows a hereditary likeness to its father", Russell wrote, "we mean that it resembles its father more closely than it does the average of the population. *The likeness is observable in respect of those [rather incidental] individual characteristics that distinguish the father from the rest of the race"* (emphasis added). Much the same can be said of the child's resemblance to its mother.

It's also possible that there will be no particular resemblance to either parent. "But yet in all three cases the child would show the characteristics of its species and its race — it would be a human child, distinguishable as belonging to the same racial type as its parents". As Russell then noted, this general resemblance in type, whereby all members of a species *share* an entire manner of development and way of being, can hardly be understood by referring to the inheritance of this or that inessential variation wherein a parent happens to *differ* from most other members of the species. But such inessential variations have been a main focus of geneticists' investigations for the past century.

The distinction between a fundamental, shared nature, on one hand, and individual peculiarities that occur *within* that shared nature, on the other, has practical implications for genetic research:

> The broad general resemblances of type give no hold for experimental or statistical treatment, and have accordingly on the whole been ignored. But it is this *general* hereditary resemblance which constitutes the main problem. [The gene theory] deals only with *differences* between closely allied forms, and with the modes of inheritance of these differences; it leaves the main problem quite untouched as to why, for example, from a pair of *Drosophila* only *Drosophila* arise. It takes for granted the inheritance of Johannsen's "great central something" — the general hereditary equipment of the species (Russell 1930, pp. 269-70).

We could also add here that the species' capacity to produce variations in offspring was drastically understated by the methods the researchers employed — a problem that continues to this day. These laboratory methods, by keeping conditions as uniform as possible, enabled geneticists to isolate more or less reliably reproducible "causes". This strengthened their conviction that biological causation could be approached on the model of the physical sciences. In other words, the experiments were designed, perhaps unintentionally, so as to reinforce pre-existing beliefs about the nature of biological causation. After all, without reliable, unambiguous, isolated causes and effects, how could one come up with a publishable paper?

What this overlooks is that every organism is a thoroughly holistic (contextual) being whose entire business might be seen as the continual redefining of its own part-relations, or causal interactions, in response to different environments. Keeping those environments constant in the laboratory was a way of repressing the full expression of the organism's character as it might have manifested under varying circumstances — a unity that could not be summed up in terms of a set of discrete and fixed causes and effects.

A vast (and almost overwhelming) amount of research today has had to be aimed at elucidating the context-dependent activity of organisms that was overlooked earlier. As a result, "context-dependent" is now a byword of genetic and molecular biological investigations (Chapter 6). And yet the pathological tendency of the earlier work, compulsively driven as it was by the effort to isolate unambiguous causes, continues to distort these newer investigations (Chapter 9).

Whole versus part

The issue here concerns the distinction between, first, individual features of an organism imagined as discrete and more or less separable parts (traits or "characters") somehow thought to be *caused* by particular genes; and, second, the integral unity whereby every organism exists and functions as a single whole. Isolated "characters" — for example, the color of a pea or of an animal's eyes — are much more easily assessed and compared in two similar organisms than are the *characters* of two whole organisms of different types. The usual genetic breeding experiments that compare differences in isolated traits of closely related organisms can hardly be applied to the different natures and ways of being of an antelope and a bison — let alone an eagle and a pig — if only because the fact of infertility between fundamentally different types normally renders routine experimental inter-breeding impossible in such cases.[2]

You might think that, given the broad fact of infertility between different types, biologists would have cast around for new approaches to the problem of an organism's inherent governing nature, even if it required quite different methods from those they were trained in. (See Chapter 12 for examples of alternative methods.) What is at stake, after all, is our understanding, not only of the organism, but also of evolution. We certainly cannot answer all the questions we have about fundamental evolutionary change — for example, questions relating to the origin of basic body plans — merely by looking at how specific gene variants correlate with differences between closely allied forms of the same general type.

The picture I have been developing in this book shows us that organisms are in fact coherent, qualitative, story-telling wholes that inform and define their own parts. The parts, being so informed, share in each other's identity and become inseparable features of a larger unity. Some such picture has been acknowledged by many biologists throughout the history of their discipline. *If the picture is accurate, then the power to maintain this larger unity across generations — which also suggests a power to transform the unity — would seem to be central to our understanding of heredity and evolutionary change.*

This is truly decisive. Have biologists in our day lost sight of the whole organism because of their fixation upon the molecular parts known as genes? And have they lost sight of evolutionary dynamics because of their fixation upon the hereditary transmission of genes rather than entire living cells?

Russell laid direct hold of this matter when he considered what it meant to realize that the activity of an organism cannot be reduced to the actions of its individual parts. If it is truly the case that the organism as a whole plays a governing role whereby it continually informs its parts with its own character and "catches them up" within its own powers of activity, then the performance of the whole "can be [hereditarily] transmitted only by a whole, i.e. by the egg in its entirety, which already at the very beginning of development *is* the new individual” (Russell 1930, p. 283).

Russell then cited a 1903 comment by the German botanist F. Noll (who was writing before the word “gene” came into usage):

> If the egg-cell of a lime tree is already a young lime tree, there is no need of any idioplasm, germ-plasm, pangens, or heredity-substance to render possible its development into a lime tree; the egg-cell *as a whole* is the heredity-substance (Russell 1930, pp. 287-88).

Material parts — or activity?

In Chapter 17 we were given one view of the whole organism. There we saw the many dramas of cell differentiation in humans. Hundreds of cell types, sometimes outwardly differing from each other as much as an eel differs from a goldfinch, are woven with almost infinite attention, intricacy, and complexity into the integral, ever-adapting unity of the organism as a whole.

Amid this diversifying whirl of cell lineages in a human embryo, where our genomes are simultaneously being summoned into the service of wildly different cellular phenotypes, we can hardly help asking: What is the unifying and coordinating source, or power, through which all the radically diverse differentiating cells are formed into coherent tissues, organs, organ systems, and the stable, functional unity of an entire human being?

To get a grip on the organizational challenge, think first of the “humble” yet extremely dynamic and context-sensitive “hair follicle niche” we looked at in Chapter 6. Then consider the unthinkable number of distinct niches, many of them microscopically small, in the liver, or in the kidney, or in the brain, pancreas, bone marrow, and every other part of the body. They are *all* extraordinarily complex. Vast numbers of such interpenetrating contexts, while mutually shaping each other, must somehow come under a global coordinating power reflecting the form and life of one human being.

The interactions within and between all these niches, organs, and organ systems look as though they are virtually infinite. Furthermore, environmental conditions and bodily activity are continually changing in an endlessly varying manner. As a result, those “virtually infinite” interactions, including the patterns of gene usage in billions of cells, are only momentary. They must be capable of being reorganized minute by minute and hour by hour.

Further, the task of global coordination goes far beyond what we normally think of as coordination. For the parts being coordinated are always in the process of becoming more or less *different parts*. We are never speaking merely about the coordination of existing parts, but also about their transformation — and, ultimately, their coming into, or passing out of, existence.

Is all this not one angle from which to view Johannsen’s “great central something”? Yet, a century after his comment few have gained the courage to contemplate this coordinating/creating power so evident in every organism, let alone to ask about its relation to inheritance. For example, regarding the wise and living capacities through which the unity of the organism is sustained, and through which the materials of inheritance are caught up into a gamete: do we not have every right to question whether these capacities can themselves be accounted for by the materials that take form through their agency?

That may seem a strange question. But there is nothing wrong with acknowledging the constrictive boundaries of our current understanding. At present we scarcely know how to speak about such matters. But we shouldn't have difficulty at least holding on to the observationally sound idea of the unity, wholeness, and distinctive character of every organism. Only by starting with what we observe can we work toward a deeper understanding. And one thing I believe we can say is this: the wholeness and character of an organism is most fully visible in its powers of directive *activity*, not in the material *results* of this activity.

On the face of it, the failure of biologists to explore the powerful explanatory potentials of the organism's more-than-genetic, whole-cell capacity for directed change seems to reflect one of the most egregious and crippling blockages of thought in all the history of science. You may recall the question put forward in Chapter 17 when we were looking at cell differentiation: Why should a forward-looking, adaptive power, manifest in all organic activity and vividly demonstrated in all the cell lineages of our bodies, cease altogether at just one decisive point: namely, the point where the germ cell lineage contributes a gamete to the next generation?[3]

If anyone is appealing to mysticism or magic, presumably it is those who posit such an otherwise unexplained hiatus in the organism's routine management of its differentiating cells. These all participate in the organism's power to move directively toward a future state that is not at all rigidly determined by its current state. It is clear that every cell, every embryo, and (as the paleontological record so strongly suggests) every population of organisms possesses a nature that not only reflects its material past, but also contains its own characteristic potentials for adaptive self-transformation.[4]

Is the principle of holism really all that difficult?

In 1978, and again in 1985, Harvard geneticist Richard Lewontin wrote that if an organism's traits are to lend themselves to natural selection, they must be *quasi-independent*. That is, they must be changeable (subject to mutation) in at least some ways that do not dramatically alter other traits. This is because any such correlative alterations are very likely to be harmful to the organism.

Think of it this way: if an organism is so thoroughly holistic that changing any one thing will change many other things, then (on the gene-centered/mutational view) evolution in the direction of greater overall fitness would require a virtually impossible combination of beneficial mutations to different parts of the organism all at once, so that they might all be selected together.[5] Such seems to be the prevailing view, anyway.

Lewontin's "quasi-independent" criterion has been picked up by others, sometimes in order to make jabs against the idea of holism. Philosopher of biology Kim Sterelny, for example, has written that “It is hard to change developmental sequences if the development of any characteristic is linked to the development of many characteristics. For a change is likely to ramify, having many effects on the developed phenotype, and some of these are nearly certain to be deleterious”:

> Thus, to the extent that development is holistic, the more complex the organism, and the more it has been elaborated over evolutionary time, the less significant further change there can be in that lineage. The point that adaptive change would be impossible if development were holistic has been made before. Lewontin, for example, has pointed out that such change requires traits to be “quasi-independent” … (Sterelny 2001).

But there is something strange here. This argument from Lewontin and Sterelny emerges from the assumption that evolution is rooted in genetic mutations that are more or less random, and therefore likely to conflict with one another. In other words, it is rooted in an assumption that the organism does *not* function integrally, coherently, and holistically. Then the argument is turned against the idea of holism that has already been denied by assumption. That’s not much of an argument.

If an organism’s life and development is holistic in the manner that has so long been recognized, why should we suddenly lose sight of this holism as soon as we turn our attention to its implications for evolution and inheritance?

Why, for example, should we abandon our faith in an organism’s holistic capacities when it comes to the preparation of a coherent inheritance for its offspring? And why should we lose sight of the developing organism’s remarkable capacity to integrate and reconcile as far as possible its various physical resources — or, for that matter, the even more stunning capacity of two gametes to organize their separate lineage inheritances (each containing many “mutations” relative to the other) into a single, viable zygote?

It seems that the very idea of holism is so alien to biologists that the attempt to think it is aborted before it gets very far. This is all the more odd given that many of those repelled by the idea of holism in general are also (and with justification) enamored of the inescapably holistic idea of *phenotypic plasticity* — the organism’s ability to alter itself in order to adapt to a particular environment. If organisms are phenotypically plastic, then their different internal systems — for example, those involved in bone growth, muscle growth, and nerve growth — must be tightly integrated, so that they can respond adaptively and mutually to changes in each other. “Phenotypic plasticity”, we read in one enthusiastic author, “pre-adapts lineages to evolutionary change, by connecting the development of distinct organ systems”:

> Limb development requires simultaneous and co-ordinated development in other organs and tissue systems: cartilage, muscle tissue and attachment points, innervation of soft tissues; circulatory connections to tissues and bone marrow. If bone structure or muscle mass is plastic, responding to signals from the environment, co-ordinated systems must be plastic too, responding to signals from the systems developing with them … This same sensitivity of integration to the contingencies of development will make functional integration possible in the face of genetically-caused changes in crucial organ systems.

The author of these remarks (Sterelny 2009) happens also to be the author of the comment above about the problem holism presents for evolutionary change. It’s as though, when one’s attention turns to evolution, one is obligated to begin thinking of change as if it were brought about, not by the character and agency of the organism, but by random disturbances to a mere aggregate of particulate genes that somehow map to and determine the organism's phenotype.

And, yes, it is then very hard to imagine a set of scattershot changes that would, in harmony, alter the intricately interwoven, holistic way of being of an organism. But once we have acknowledged an organism's holistic nature — and, in particular, its capacity for holistic, adaptive change — why should we so quickly forget it, especially when, in evolutionary theory, we are actually addressing the issue of holism?

Perhaps Sterelny changed his mind between the writing of those two articles. In any case, I am not here saying anything about the degree of "quasi-independence" some organismal traits might have. Nor am I suggesting that evolution is equally possible for all species. For all we know, physically evident evolution may no longer be occurring in humans — or not occurring nearly as much as in previous evolutionary eras. It might be argued, after all, that in humans a major evolutionary transition is placing the power to direct evolution into our own hands. And this looks more like an evolution of consciousness than a further bodily evolution.[6]

As for "quasi-independent" traits and holism, I think Samuel Taylor Coleridge, writing during the first half of the nineteenth century, put the question into the right perspective:

> "The living power will be most intense in that individual which, as a whole, has the greatest number of integral parts presupposed in it; when moreover, these integral parts, together with a proportional increase of their interdependence, as *parts*, have themselves most the character of wholes in the sphere occupied by them" (Coleridge 1848).

Or, re-phrased: Life will be fullest in the individual that most fully integrates the greatest number of parts; and when those parts are themselves most like wholes. We can glimpse the unity underlying these apparently contrary principles when we realize how, in human society, an ever stronger and more centered self is required if we want that self to contribute ever more strongly and selflessly to the good of the larger society.

Or think of your heart or brain. These wonderfully "perfected" organs, while possessing the strongest possible identity and wholeness in their own right, are — as an expression and extension of their wholeness — bound together with everything else that goes on in the body. No part of our bodies can be separated from the circulatory and nervous systems, just as the functioning of the heart and the brain cannot be separated from the other parts of our bodies.

In other words, the potential for holism and the potential for a (relatively) independent perfection of parts are two sides of the same coin. An overall, deeper holism depends on a greater independence and perfection of parts in their own right, and a greater independence and perfection of parts depends on a deeper holism. The two principles do not push in opposite directions, but are complementary, with each requiring the other.

Coleridge's remark derived, I believe, from a straightforward observation of living beings and required no evolutionary theorizing. He was, of course, writing before Darwin's *Origin*. And he was willing to look at whole organisms as they actually presented themselves. There is nothing in evolution that contradicts the most profound holism of organic life, which is in turn what makes evolution possible.

Where are we now?

When the Organism Was Seen Whole

Two paragraphs from this chapter capture, I think, its most salient thought while also pointing strongly toward Chapter 25 where I try to articulate, as best I am capable, “Some Principles of Biological Understanding”:

> Amid this diversifying whirl of cell lineages in a human embryo, where our genomes are simultaneously being summoned into the service of wildly different cellular phenotypes, we can hardly help asking: What is the unifying and coordinating source, or power, through which all the radically diverse differentiating cells are formed into coherent tissues, organs, organ systems, and the stable, functional unity of an entire human being?
>
> Regarding the wise and living capacities through which the unity of the organism is sustained, and through which the materials of inheritance are caught up into a gamete: do we not have every right to question whether these capacities can themselves be accounted for by, the materials that take form through their agency?

During the first half of the twentieth century a considerable number of biologists, among whom E. S. Russell was a leading figure, sought to articulate a biology that kept the whole organism in view. We could, perhaps, call theirs a “common-sense view” since, as I argue throughout this book, all biologists even today reveal in their direct, observational language that they see the truth of the agential organism — its story-telling, directive, *telos*-realizing life — in a perfectly practical sense. (See Chapter 2, “The Organism’s Story”.)

A key point emphasized here is that inheritance is never anything other than whole-cell inheritance; we always find ourselves watching the uninterrupted life of whole, living entities. It happened, however, that the possibility of tracking and statistically analyzing the passage of genes from one generation to the next offered a possibility for the kind of logically clear, mathematized results that felt to most biologists “more like science” than did the difficult effort of acquainting themselves with the less clear-cut, qualitative character of whole cells and whole organisms.

And yet, as Russell pointed out, this narrowed the biologist’s view down to the observation of some of the genetic causal factors playing into more or less minor differences between closely allied organisms, such as parents and their offspring. (Geneticists also learned to produce monstrosities by grossly interfering with normal development, but these didn’t have a whole lot to teach us about the evolutionary potentials of viable organisms.) On top of this, geneticists blithely ignored the multicellular organism’s dramatic capacity to orchestrate the “evolution” (differentiation) of numerous cell lineages that are, in their own terms, as phenotypically distinct as distantly related species.

In the next chapter (which can usefully be read in close conjunction with this one) I will try to pinpoint the decisive inclinations underlying the “genetic distraction” that has so powerfully wrenched the past century's evolutionary biology away from any reckoning with the actual life of whole organisms.

Notes

1. On the relevance of Russell's work today, see "Heredity, Development and Evolution: The Unmodern Synthesis of E. S. Russell" by Maurizio Esposito (2013). For a view of Russell along with W. E. Ritter, Kurt Goldstein, Agnes Arber, and J. H. Woodger, see "A Reflection on Biological Thought: Whatever Happened to the Organism?" by Robin W. Bruce (2014).

2. Hybridization does in fact sometimes occur between distinctly different species (within limits) and, as I mentioned in Chapter 19, it is possible that this contributes to rather dramatic evolutionary change. But such hybridization is likely to generate massive genetic and cellular reorganization, far too extensive and global to allow for conventional genetic approaches. So one is still facing the unsolved "problem of the whole" — the problem that genetic analyses were designed to steer clear of by focusing on particular genes causing particular trait differences under well-defined conditions.

3. Evolutionists are interested in germline (heritable) genetic mutations as the primary basis for evolutionary change. Yet no one will quarrel with the fact that we lack any such germline mutational basis for the very great changes that can occur in the differentiating cell lineages of a complex, multicellular organism. But some biologists do reasonably ask whether there are non-germline ("somatic") mutations along the various paths of cellular differentiation, and whether these play some role in the processes of differentiation. The question is being actively explored today.

Even before the matter is elucidated, however, we can say this much: to whatever degree somatic mutations do occur and are important to cell differentiation, the fact would show only that the organism manages and directs its own genetic mutations. Why? Because cell differentiation (and development in general) are such obviously *directive* processes, and are universally recognized as such. If mutations turn out to be an essential part of these processes, it will show that they do not play their roles in a random manner, but rather find their place within the larger coordinated activity.

4. I have never heard an evolutionary biologist even acknowledge the *possible* legitimacy of an inquiry into the heritable, whole-cell, transformative capacity of germ cells or gametes. They certainly do not seem inclined to cite evidence for anything of the kind, or even to pay much attention to the fact that the development and specialization of the germ cell lineage is at least as dramatic and well-directed as the differentiation of any other forward-looking cell lineage in complex organisms (and *all* differentiating cell lineages are forward-looking).

But, just as important, the claim of "no evidence" for more-than-genetic, whole-cell inheritance, when it is made, usually reveals itself as spectacularly circular, being based on the argument that, whatever the whole-cell transformation we witness in germ cell lineages, we don't see corresponding changes in the genetic sequence. That's the argument that surfaces so often when the question of transgenerational epigenetic inheritance is raised. In other words, an insistent *assumption* that all heritable change must take the form of germline genetic mutations — or at least be closely analogous to them — is being used to refute the claim that there is more-than-genetic, whole-cell, heritable change. (See Chapter 22, for a discussion of the curious idea that evolutionary change depends on the stability — unchanging nature — of already achieved mutations.)

When confronted with the problem of the character of the whole cell, biologists have a tendency to cite the impossibility of carrying out their usual analyses wherever one insists on speaking of "wholes". (See the immediately following section.) And so there has never been a major research program aimed at tracking how whole-cell inheritance might play into evolution. The most obvious possibility is the least considered — not because it is faulty, but only because it is difficult.

5. See Lewontin 1978 and Levins and Lewontin 1985. In the latter work the authors wrote:

> By quasi-independence we mean that there exists a large variety of paths by which a given character may change; although some of these paths may give rise to countervailing changes in other organs and in other aspects of the ecological relations of the organism, in a reasonable proportion of cases the countervailing effects will not be of sufficient magnitude to overcome the increase in fitness from the adaptation. In genetic terms, quasi-independence means that a variety of mutations may occur, all with the same effect on the primary character but with different effects on other characters, and that some set of these changes will not be at a net disadvantage (p.80).

6. German philosopher, Dieter Wandschneider, has commented that "In a world in which sickness can effectively be cured, clinics and spas are at people's disposal, artificial limbs are applied, and replacement organs are implanted, the biological principle of [Darwin, in its modern form] has been 'unhinged'":

> One could object that the human species changes biologically even today — for example, in muscle structure, susceptibility to sickness, and life span. That cannot be denied. But these changes are manifestations of the "self-domestication" of man and thus consequences of civilization, which as such are not the results of *natural* selection. On the contrary, they are expressions of an evolution that is now taking place under completely different conditions, namely those of *cultural evolution* (Wandschneider 2005, p. 204).

Sources

Bruce, Robin W. (2014). "A Reflection on Biological Thought: Whatever Happened to the Organism?", *Biological Journal of the Linnean Society* vol. 112 (June), pp. 354-65. doi:10.1111/bij.12188

Coleridge, Samuel Taylor (posthumous/1848). *Formation of a More Comprehensive Theory of Life*, edited by Seth B. Watson. London: John Churchill. Facsimile edition from Ann Arbor MI: UMI Books on Demand.

Esposito, Maurizio (2013). "Heredity, Development and Evolution: The Unmodern Synthesis of E. S. Russell", *Theory in Biosciences* vol. 132, no. 3 (September), pp. 165-80. doi:10.1007/s12064-013-0177-4

Johannsen, Wilhelm. (1923). “Some Remarks about Units in Heredity”, *Hereditas* vol. 4, pp. 133-41.

Levins, Richard and Richard Lewontin (1985). *The Dialectical Biologist*. Cambridge MA: Harvard University Press.

Lewontin, Richard C. (1978). “Adaptation”, *Scientific American* vol. 239, no. 3 (September), pp. 212-30.

Oyama, Susan, Paul E. Griffiths and Russell D. Gray, editors (2001). *Cycles of Contingency: Developmental Systems and Evolution*. Cambridge MA: MIT Press.

Russell, E. S. (1930). *The Interpretation of Development and Heredity: A Study in Biological Method*. Reprinted in 1972. Freeport NY: Books for Libraries Press.

Sterelny, Kim (2001). “Niche Construction, Developmental Systems, and the Extended Replicator”, in Oyama, Griffiths and Gray 2001, pp. 333-49.

Sterelny, Kim (2009). “Novelty, Plasticity and Niche Construction: The Influence of Phenotypic Variation on Evolution, *Mapping the Future of Biology*, pp. 93–110. doi:10.1007/978-1-4020-9636-5_7

Wandschneider, Dieter (2005). “On the Problem of Direction and Goal in Biological Evolution”, in *Darwinism and Philosophy*, edited by Vittorio Hösle and Christian Illies, pp. 196-215. Notre Dame IN: University of Notre Dame Press.

CHAPTER 21

Inheritance, Genetics, and the Particulate View of Life

This chapter about the gene-centered (“genocentric”) view of evolving organisms shouldn’t have needed to be written. Today genocentrism has been challenged from so many different sides, by so many leading biologists, and in such an ever more insistent manner, that it might easily seem a waste of time to raise the usual issues afresh here. So I won’t.[1]

But there are caveats. One is that, despite the criticism, the idea of the masterful, controlling gene remains as strongly entrenched as ever in the minds of most biologists. This is especially true of evolutionary theorists, for whom the word “genetic” has long been synonymous with “heritable”. In other words, for purposes of evolutionary theory genes substitute for the entire, one-celled living being that passes between generations. This means that, as participants in an inheritance-based evolutionary lineage, organisms themselves scarcely exist for the theorist.

The century-long habit of genocentrism is seemingly resistant to all criticism. As three Duke University biologists summarized the matter in 2017, “Everyone understands” that the idea of a definitive *gene for* this or that feature of an organism “is a distortion of the biological facts, yet, as a profession, we have yet to rid ourselves of this crutch” (Gawne, McKenna and Nijhout 2018).

Much of the criticism of genocentrism has arisen from the field of evolutionary-developmental biology (“evo-devo”). Yet even here, according to a leader in that discipline, “increasing gene centrism characterizes the field today”:

> This reductionist attitude continues to be upheld, even though overwhelming evidence points to the fact that it is not gene expression and regulation that singularly define body structures but the systemic processes of interaction between genes, cells, and tissues as well as the physics and physiologies of the involved entities and their interactions with numerous factors of the environment (Müller 2019).

A second caveat, even more discouraging, is that the critics themselves leave the door wide open for the persistance of genetic reductionism. This is because few if any well-positioned, reputable biologists are willing, at the risk of reputation and career, to speak out against the reigning materialist dogma of their profession.[2]

What isn’t generally recognized is that this dogma invites, as an inevitable counter-movement, an almost worshipful regard for the all-determining, informational gene — a machine-like gene intelligently designed and engineered from outside by the “creative forces” of evolution. In this way the theorist employs the gene as a lifeless stand-in for the present and effective wisdom that moment by moment lives and expresses itself in every animal’s inner, qualitative, perceptual experience and in its thought-full response to that experience.

In what follows I will review the genocentrism of the received evolutionary theory, and then explore some fundamental problems with genocentrism — problems the present critics of genocentrism cannot allow themselves to recognize at risk of violating the materialist taboo. This exploration will continue into the next chapter, where we will look at the contrast between the evolutionarily stable ("potentially immortal") genetic particles that Richard Dawkins celebrates so vehemently, and the evolutionarily stable *yet dynamically transformative* whole organism.

DNA as the essential substance of evolution

As we saw in Chapter 16 ("Let's Not Begin With Natural Selection"), evolution is said to be inevitable once three conditions are met: (1) There must be trait *variation* among individuals in a breeding population; (2) This variation must to some degree be *inherited*, so that offspring generally resemble their parents more than they resemble others; and (3) Individuals possessing different variants of a trait must, at least in some cases, exhibit *differential fitness* (or differential survival) — that is, they must produce, on average, different numbers of offspring, whether immediate offspring or later descendents. This is often referred to as *survival of the fittest*, or the principle of *competition*.

We also saw in that earlier chapter that these three conditions — insofar as they are abstracted from the life of the organism and its agency — become a hollow formula that tells us nothing about why a species evolves in the direction it does. That is, until we reckon with what organisms *do* as a function of their entire way of being, the so-called "core logic", or "algorithm", of evolution can tell us nothing at all about their evolution or about the diversity that may arise from them — or even about whether they will evolve at all. And when we do reckon with the active life of organisms, it is this reckoning itself, not some core logic of inheritance and selection, that elucidates the evolutionary trajectory of a species.

The chief excuse for ignoring what organisms do has been found in a distorted picture of genes and DNA. This picture gives to the core logic described above what little appearance of biological content it has:

- **Variation:** All or nearly all the variation that matters for evolution (so the theory goes) is ultimately accounted for by mutations in the genetic sequence.
- **Inheritance:** So far as it bears on evolution, inheritance equates completely or nearly completely to the replication and transmission of genetic sequences.
- **Differential fitness:** The organism's differential fitness, so far as it matters for evolution, is regarded primarily as the result of traits that in turn result from instructions carried by genetic sequences.

So genes are the one unquestioned material foundation and efficient cause upon which, from the organism's side, the modern edifice of evolutionary theory has been erected. As defined in a classic introductory text, the process of evolution "includes all mechanisms of genetic change that occur in organisms through time..." (Hartl 1988, p. 143). Evolution, in this view, looks very much like a matter of genes and their fate — and not much more.

The aggressive claims of population geneticists

The author of that last quotation was a population geneticist, and it was preeminently the population geneticists who framed the twentieth-century “Modern Synthesis” as the definitive formulation of evolutionary theory. It is likewise the population geneticists who still today speak most forcefully about the primacy of genes. And it is the population geneticists (regarding themselves as working at the pinnacle of evolutionary theory) who continue to dominate the evolutionary field today, if only by virtue of their long-established control over the institutional levers of power.

Their life’s work has always centered on calculations relating to the transmission of genes between parents and offspring, and the changing distribution of genes within populations. The more advanced, technically impressive results of this work often take the form of sophisticated equations that tend to be more or less opaque to working biologists outside the field of population genetics.

Here are two examples of comments from population geneticists:

Michael Lynch, who holds the Distinguished Professorship of Evolution, Population Genetics and Genomics at Indiana University and was formerly president of the Genetics Society of America, has remarked that “the litmus test for any evolutionary hypothesis must be its consistency with fundamental population-genetic principles”. He freely admits that organisms themselves, as “phenotypic products”, result from “more than a change in gene frequencies”. But the crucial conclusion remains, if only by brute assertion: “If we are concerned with the process of evolutionary change, then evolution is indeed a change in genotype [gene] frequencies” (Lynch 2007a; Lynch 2007b, p. 371).

And then there is Dan Graur, author of a textbook on *Molecular and Genome Evolution*, who proceeds in the same confidently dogmatic spirit (to which he adds his own unique brand of arrogance, in which — judging by the larger body of his work — he apparently revels):

> Evolutionary biology is a mature science. It is a coherent discipline with a handful of logical principles, each of which repeatedly withstood rigorous empirical and observational testing. Evolution is not difficult to define. If one ignores the obfuscations of the creationists, the casuistry of the philosophers, and the ruminations of the “sophisticates,” evolution turns out to be merely the process of change in allele [gene] frequencies over time. The only mandatory attribute of the evolutionary process is a temporal change in allele frequencies (Graur 2015).

This is truly amazing — a stunning contraction of human understanding among the would-be elder statesmen of evolutionary theory, smugly satisfied that they do indeed sit at the pinnacle of their discipline. The organism’s entire way of being along with its needs, interests, and agency have been reduced, for purposes of evolutionary theory, to one material part — DNA. The underlying drive appears to be the reduction of mindedness to mindlessness, *logos* to meaninglessness, *telos* to chance — all reflecting a horror of interiority.

The habit of ignoring organisms is so stubbornly entrenched among population geneticists that their ability to recognize crucial evolutionary issues seems scarcely to exist. Think, for example, of the problem of the origin of innovation — that is, the problem of the "arrival of the fittest", or the arrival of new, living performances (traits) for natural selection to act upon. (We looked at this in Chapter 16.) Armin Moczek, a prominent evolutionary developmental biologist at the University of Indiana, remarked that "fields such as population-genetics have long stopped asking the question how evolution innovates, not because it is not a foundational question in evolutionary biology, but because population genetics lacks the ability to even frame the question" (Moczek_2022).

They have stopped asking in part because the fact that genes can make a more or less stable difference in existing traits (Chapter 22) has convinced them that they need not consider all the other, less experimentally and mathematically tractable features of an organism's life that also make a difference. Nor need they inquire into the principles of organization through which cellular and organismal identity are stably maintained, and through which alone a trait can come into existence as an integral and viable aspect of the larger whole. And they are least of all inclined to consider whether the organism's most dramatically demonstrated capacity — its capacity for directed developmental change and metamorphosis consistent with its own way of being — might be relevant to evolution.

Who defines what counts as an evolutionary process?

The population geneticists, in the manner of those adhering to many an aging and rickety scientific viewpoint, have constructed for themselves an institutional and intellectual fortress whose final crumbling must, as the rather brutal saying has it, await the dying out of its last, well-known defenders.

In the meantime, one thing giving a sense of impregnability to the fortress is the fact that evolution has been aggressively *defined* in terms of genes, as we heard above. One is then bound to argue that whatever is not adequately gene-like cannot be important for evolution.

This argument by definition is why population geneticists routinely dismiss epigenetic factors (Chapters 7 and 14) as irrelevant to evolution: such factors, they tell us, often don't have the long-term, transgenerational stability usually ascribed to genes, and therefore can't contribute much to evolution.[3]

In other words, "Since epigenetics doesn't give us the kind of genetic stability we want to see as the essence of a mindless sort of evolution, we refuse to consider what evolutionary potentials it *does* give us". Those who think this way can scarcely imagine that epigenetics presents us with a revealing expression of the highly adaptive processes of continual, directive change we discover in every sort of whole-organism activity — for example, in the many differentiating cell lineages of our own developing bodies. These lineages result from the changing organization of whole cells, which includes their changing ways of employing their genes.

Such transformative processes — which one might think would be the first things looked for by evolutionists — are ruled out of evolutionary theory on the grounds (now known to be false) that nothing occurring in development affects the *genetic* inheritance of the next generation. But even if that were true, so what? It overlooks the entire nature of cellular inheritance during cell differentiation. This inheritance is not only dramatic, but undeniably a *whole-cell* phenomenon. If biologists dismiss the significance of developmental processes for evolution, it is only because they have planted their flag and staked their claim in advance: "We're not interested in the potentials of the whole cells that contribute an inheritance to the next generation, but only in the genes those cells contain".

As with so many perverse doctrines, there is a dim and distant reflection of the truth in the gene's-eye view of evolution, although it is a truth lost on Lynch, Graur, and their kin. DNA is indeed caught up in, and informed by, the character of the whole organism, including its adaptive character. Therefore we can in one way or another expect to find the whole organism reflected in DNA. Such is the case with all the other major aspects of any organism, as we have already seen in our discussion of cell membranes and the cytoskeleton (Chapter 4).

Getting to the bottom of things?

One of the most common strategies for honoring the materialist taboo in all sciences is to describe a microscopic level of meaningless and inherently inert, mindless things, or particles, possessing fixed, well-defined natures with causal powers. (The fact that causal powers are *powers*, not things — so where in the material world do *they* come from? — is conveniently ignored.) Then one claims that whatever really counts in the explanation of phenomena derives from various effective combinations of these particles.

In Richard Dawkins' biological theorizing, the particles at issue are genetic elements with a wonderfully computational nature. "Digitalness", he has said in what must have been one of his rashest statements, "is probably a necessary precondition for Darwinism itself to work" (Dawkins 2006, p. 163). "What is truly revolutionary about molecular biology", he wrote, "is that it has become digital". We know that genes "are long strings of pure digital information … The machine code of the genes is uncannily computerlike. Apart from differences in jargon, the pages of a molecular-biology journal might be interchanged with those of a computer-engineering journal" (Dawkins 1995, pp. 17-19).

The meaning of "digital" can be illustrated by the game of basketball. The game is so designed that the making of a basket is always definite and unquestioned. The ball either goes through the hoop, or it does not. A team either earns points for the basket or it does not. How graceful or awkward, skillful or random the shot may have been has no bearing on the matter. A player's approach to the basket can be ugly as sin, but if the ball ends up going through the hoop, the points are counted. There's a clean, yes-or-no, "ones-and-zeros" aspect to the proceedings. The number of points earned is always exact and countable. Everything is precise, and there is no ambiguity.

Dawkins' claim accordingly is that, when it comes to the identity and role of genetic particles, "there are no half measures and no intermediates or compromises" — certainly nothing we might recognize as a power of self-transformation. "Our particles of inheritance …

don't blend, but remain discrete and separate as they shuffle and reshuffle their way down the generations" (Dawkins 2006, pp. 159-63).

So this is what Dawkins assumes to be the essential character of our genetic material, which he situates at the causal bottom of every organism: it consists of discrete and separate causal elements that do not interpenetrate, neither are they subject to half measures, intermediates, or compromises. His reference to genes as strings of "pure digital information" makes it clear that his "causal" factors come very close to being elements of computer logic.

The convergence of the two ideas of (1) causal force and (2) compelling, computational logic in Dawkins' mind — a symptomatic conflation running through much biology today — is ironic in light of his materialist commitments. If in fact the pure conceptuality of logic finds revelatory application in science, it would only reveal a world causally governed or organized according to thought. The only problem is that, whatever we may say about the inanimate world, the very real mindfulness we encounter in our concrete and engaging interactions with organisms is far more profound — and far less one-dimensional — than a mere play of abstract logic.

It hardly needs saying that Dawkins' genetic informational bits are, by definition, incapable of participating in living wholes. Because their identity is conceived as almost eternally fixed and quantifiably (digitally) specifiable, they cannot lend themselves to being qualitatively transformed or reimagined in harmony with the fluid, organizing ideas and intentions at work in every organism.

But Dawkins gets his digital, non-blending particles of inheritance only by defining them into existence. Reality gives us a very different story.

How the image of "particles" has distorted the biologist's imagination

Digital, unblending genetic elements of pure, computational *logic* or *information*: where is one even to begin a critique of these impossible notions, upon which so much contemporary evolutionary theory is erected? Where in the living organism do we find the slightest justification for them? Can Dawkins show us even one DNA sequence that functions in a strictly digital fashion?

We might start thinking about this at a fairly remote distance from Dawkins' immediate genetic meanings by looking at an illustration offered by twentieth-century cell biologist, Paul Weiss. He reminds us of the commonplace pictures and models of molecules, represented as conglomerates of colored, spherical "billiard balls", each standing for an atom, and each seeming to be a stable, self-contained unit. He then contrasts that with the image in Figure 21.1, which shows how the constituent atoms of a molecule interpenetrate ("blend" into) each other as continuous fields or a complex system of mutually shaped forces. These "blur the former sharpness of the outer boundary of the molecule and let it melt into the surrounding molecular domains" (Weiss 1971a, p. 9).

Weiss also remarks of figures such as this that "one is reminded of the contour maps of mountain ranges. Domains of particles are no more truly isolated than are mountain peaks"

(Weiss 1971b, p. 235). Moreover, the parts of such an interactive system are rather "like islands", so that they must be "conceived as interconnected, though not so solidly as by a bed of rock, but loosely by the all-pervading mesh of forces and interactions" (Weiss 1971a, p. 11).

This may remind us of the discovery (mentioned in Chapter 5) of how water interacts with DNA. Lifting one paragraph from that earlier chapter:

> Early efforts to develop a computer simulation of a DNA molecule failed; the molecule (in the simulation) almost immediately broke up. But when [the researchers] included water molecules in the simulation, it proved successful. "Subsequent simulations of DNA in water have revealed that water molecules are able to interact with nearly every part of DNA's double helix, including the base pairs that constitute the genetic code".

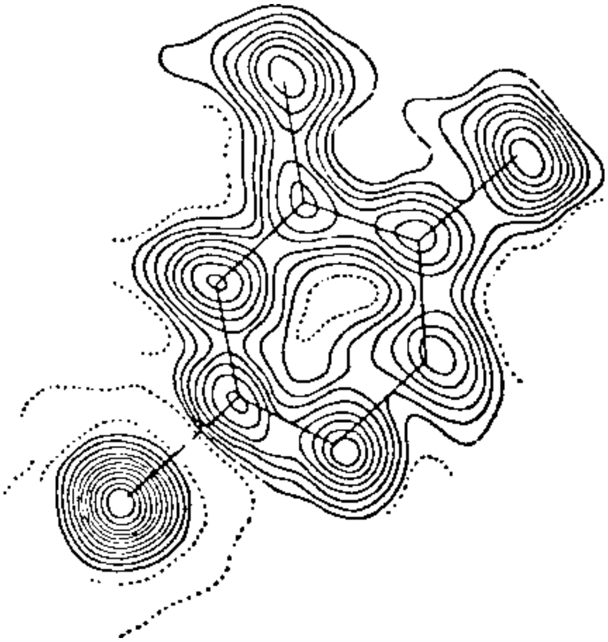

Figure 21.1. Schematic representation of a molecule, where concentric "circles" are intended to map electron distributions of individual atoms, and straight lines artificially represent bonds between the atoms.[4]

Needless to say, this interaction of DNA with water alters the entire landscape (or seascape) of DNA, very much in the manner of Figure 21.1 above. None of it suggests much of a defense "at the bottom" for the idea of independent, digital, unblending genetic particles. But this point will become more explicit and more directly aimed at genes as we move along.

The fundamental reality of the matter was already glimpsed in the nineteenth century by the great experimental physicist, Michael Faraday. He recorded his prescient, "final brooding impression" that "particles are only centres of force" and that, for instance, water does not consist of atomic particles "side by side", but rather of "spheres of power mutually penetrated". And in notes for a talk given to the Royal Institution, he suggested that "matter is not merely mutually penetrable, but each atom extends, so to say, throughout the whole of the solar system, yet always retaining its own centre of force" (quoted in Barfield 1971, pp. 201n11 and 244n17).

Facing up to the gestural reality of DNA

What, then, do we see when we take even a cursory look at DNA? Exactly what Faraday and Weiss would have expected.

We have already heard about the positive and negative supercoiling of the double helix (Chapter 3). Both reflect a dramatic re-organization of forces along the DNA molecule — forces from which neither genes nor single nucleotide bases (“letters”) of DNA can claim to be immune. These forces are not respecters of the boundaries between genes, and their reshaping effects are known to help determine the functional role of genes within the organism.

But supercoiling is only one of many ways the genome is continually restructured. The DNA molecule, while inherently rather stiff and inert, lends itself, under cellular influences, to endless, plastic, structural change, both subtle and not so subtle. Consider, for example, the many protein transcription factors that come to bear upon gene expression. In the simplistic thought of an earlier day, they were assumed to be just about the sole factors implementing the rigid “control logic of the genetic program”. Moreover, they were said to bind DNA in a manner strictly determined by the abstract sequence of DNA “digital letters”, rather than by gesturally engaging in a mutual dance with the plastic matrix of physical forces constituting the reality of that sequence. The determining role of the abstract sequence was then supposed to justify the geneticists’ belief that genes were the real agents in control of their own expression. But this conclusion sounds farcical today.

Transcription factors are now well known to contribute their own forces to the infinite variations in the way genetic sequences “blend” together with each other and with innumerable regulatory molecules. Actually, even within the terms of the earlier view, there were all sorts of unanswered questions about transcription factors. For example, what determined when and how often a particular factor was bound to the supposedly controlling DNA sequences? Why did it bind more to some of those sequences and less to others? And how was its activity coordinated with that of the many other transcription factors participating in the complex task at hand, which might involve the need for balanced expression of hundreds of genes?

Beyond this, however, the old concept of transcription factor binding (or not binding) to DNA is now recognized as hopelessly one-dimensional. The reality of DNA is difficult to think of as anything other than a play of ongoing *gestural form* orchestrated by the cell as a whole. You don’t need to know the complex details of the terminology in order to get a sense for what it means when an article in the journal *Nature* reports how transcription factors interact with “shape features of the DNA sequences, such as minor-groove width, roll, propeller twist and helical twist” (Burgess 2015). These ever-changing shape features are subject to influences arising from the limitless cloud of regulative molecules (including water molecules, as we heard above, as well as the transcription factors themselves) that more or less transiently swirl around a cell’s DNA. None of the analog shape features looks very much like Dawkins’ concept of digital or computer-like elements of a genetic program.

The vast majority of our DNA is tightly and forcibly bent so as to wrap around millions of nucleosome core particles in the cell nucleus. The nucleosome, as we saw in Chapter 14 (“How

Our Genes Come to Expression”), is perhaps the central integrator of signals bearing on gene expression and coming from all corners of the cell.

The wrapping of DNA around these protein core particles is probably never exactly the same in the case of any two of the thirty million or so nucleosomes in our genome, nor ever the same at any two different times in the case of a single nucleosome. The bending and shape changes in the DNA require a great variety of force interactions between DNA and the core particle, all in the presence of numerous associated molecules. So we hear (as before, in the case of transcription factors) that the functionally critical spacing and location of nucleosomes along a stretch of DNA can vary, depending on transient DNA features imposed by the cell “such as propeller twist, opening, electrostatic potential, minor groove width, rise, stagger, helix twist, and shear and roll ... and buckle” (Kurup 2019). Everything is subject to dynamic variation.

The gestural form we are looking at in the case of DNA and related molecules appears to have no limit in its extent or its significance for the cell. It cannot even be said that the double helix is always even close to being a standard double helix, or a double helix at all:

> Alternative conformations (including left-handed DNA, three-stranded triplex DNA, four-armed cruciforms, slipped-strand DNA with two three-armed junctions, four-stranded G-quadruplex structures and stable, unpaired helical regions) can exist in the context of chromosomes. Rather than being a static helix, DNA possesses dynamic flexibility and variability, as evidenced by helix regions that can be curved, straight or flexible. Differences result from variations in base stacking and twist angles inherent in different DNA sequences. DNA supercoiling [induced, for example, by transcriptional enzymes], particularly unconstrained supercoiling,[5] plays a major part in the dynamic flexibility and topological contortions of the DNA double helix (Sinden 2013).

Everything we have been hearing about is fundamentally qualitative and gestural rather than digital, and it counts not only toward whether a “basket is scored” (a gene is expressed), but also toward the “size of the score” — for example, will there be a large, rapid burst of expression, or a low-level, steady-state expression? There is also the question of the *nature* of the score: for example, which of several functional variants of a protein will be synthesized? So the qualitative, gestural features mentioned above bear hugely on the practical meaning of a gene for the organism. They help to define what any given gene is.

DNA, when caught up within the whole cell, is a phenomenon of movement. Of the endless variety of its movements, two are referred to as “DNA breathing”. One of these (which we heard about in Chapter 3) involves the rhythmic loosening of parts of the double helix from the nucleosome core particles around which they are wrapped. This has a great influence on the accessibility of portions of the DNA to gene-regulatory proteins. The other sort of breathing consists of local, transient separation of the two strands of the DNA double helix, which also affects the accessibility of the DNA.

Furthermore, the foregoing represents only a minuscule introduction to all the ways gene expression turns out to be a fluid, non-digital, and non-machinelike expression of dynamic, gestural form. I have not even mentioned what is widely considered to be the most prominent way DNA “letters”, or nucleotide bases, are modified and the play of forces re-sculpted — namely, by the attachment of methyl groups to nucleotide bases in a process called “DNA methylation”. This is the most common of a fair number of modifications to DNA, affecting many millions of nucleotide bases in our genomes. By this means the letters become *different letters*.

Neither have I mentioned the large range of factors affecting the structure of RNA, an essential molecular carrier of the “genetic code” whose liveliness of functional form is, if anything, even more obvious than what we see in DNA.

And, perhaps most important of all, I have not cited the massive research effort today dealing with the form and movement of chromosomes — for example, the critical looping movements that bring genes and regulatory elements of DNA into functional proximity within the three-dimensional space of the nucleus. We are looking here at a gestural performance that many investigators can hardly resist referring to as a “dance” or an elaborate “choreography”. We encountered some of this in Chapter 3 (“What Brings Our Genome Alive?”). How that dance occurs critically shapes how genes will be expressed. Genes are as far from being discrete, well-defined, independent causes as two ballet dancers engaged in a *pas de deux*.

A gene that, within the full contextual life of the organism, can be interpreted as a determinate cause or a bearer of strict digital logic does not exist.

To view from the bottom or view from the top?

Evolutionary theorists, so it appears, have great difficulty recognizing as significant either the stable and highly distinctive character of the whole cell and whole organism, or the remarkable interior capacities through which that character is consistently expressed and sustained amid all the transformations of individual development. And so they find it easy to discount everything living. They discount, that is, the future-directed powers of self-realization, adaptation, and whole-cell (whole-organism) reproduction — the very powers that hold the most obvious relevance to inheritance and evolution.

Organisms as such simply don’t show up through the death-shroud that is the particulate view of life. As for the particles themselves — the supposedly unblending, unexpressive, qualitatively inert genes and nucleotide bases (“letters”) — they are, in reality, illusions. The upshot of the foregoing discussion is that the discrete, non-blending, genetic particles that Dawkins, for example, is so quick to idealize as controllers of the organism’s evolution do not actually exist as real, material entities. They exist only as logical or digital constructs abstracted away from the living cell.

The situation can also be summarized by saying that evolutionary biologists are currently blind to organisms as beings *organized from within*. To speak of interiority is anathema to them, and therefore any genuine recognition of *organizing ideas* is also anathema. Which is too bad, because either the material world is such that organizing ideas have real consequences, or else the terms biologists *do* so freely use — “organizers”, “organization”, “self-organization” — are symptoms of shamefully vacuous theorizing.

Think of it: take away the organizing *ideas*, and what would be left of any sort of "organizing" or "organization"?[6] (Or, for that matter, what would be left of any science?) "Imposing a kind of *meaningful* coherence" is just what the word "organizing" means.

Consider the much-criticized but still endemic idea that there are *genes for* particular traits. If we believe that genes possess, in their own right, the essential, organizing or directing power to realize traits — traits that are in fact qualitative, non-discrete, interpenetrating, and expressive of a specific (species-related) "way of being" — then we are ascribing to genes a living power to *organize* almost unthinkably complex physiological processes requiring a kind of moment-by-moment active judgment governing a virtually infinite number of molecular interactions in a fluid, continually changing context. (I focused especially on such processes in Chapter 8).

Genes surely do *participate* in such a power, but it is a power of activity belonging to the whole organism and is not properly attributed to any collection of material elements, such as genes, that are caught up in it.

Those who want to adhere to materialist principles gain nothing by contradicting them. They gain nothing, that is, by transferring the interior, organizing ideas of the cell or organism to genes. If genes really possessed their own "informational" powers for sensing their wider context; if they really could encode messages tuned to moment-by-moment changes under infinitely varying circumstances; if they really had a way to direct the interactions among countless billions of molecules in a fluid medium, enabling those molecules to carry out indescribably intricate operations such as RNA splicing (Chapter 8); and if in general they really were able to *inform* and *organize* the life of the entire cell[7] … well, once we have accepted this impressive play of wisdom through a material genome conceived in a particulate manner, what reason would remain for denying it to the vividly expressive cell or the whole organism, where in fact we observe it?

If "context matters", as so many biologists are now telling us, it can only be because it really does substantively matter. It makes a difference to what happens. The context exercises, in other words, its own, over-arching sort of causal power. It's not a kind of power that can be transferred to materialistically conceived particles — particles abstracted from cell and organism as if they they carried a decisive causal logic independent of the living matrix in which they find their real existence.

WHERE ARE WE NOW?

Looking Beyond Particulate Inheritance

Biology today is governed by a taboo: *The biologist must never acknowledge stepping outside the materialist framework — or at least must remain unaware of doing so*. She must never grant that animals have an interior — that every animal is an integral, unified whole possessing, or possessed by, an active, wise agency.

The biologist's materialist commitments are impossible to keep. They would render the organism, as a living being, invisible to scientific investigation. This is why biologists can hardly avoid preserving the organism's agency by covertly transferring it to special molecules (DNA). But at the same time — in order to keep an illusion of observing the taboo — they speak of these wonderfully effective, "informational" molecules as if they were "things" uninformed and ungoverned by the agency of the whole.

This double-talk, which would have DNA possessing the creative powers of life while at the same time consisting of "mere chemical stuff", is somehow easier to stomach in the case of molecules than in the case of whole organisms. Molecules, being non-phenomenal (invisible to sense perception), lend themselves more obligingly to the projection of our mechanistic/animistic fantasies.

It is population genetics, above all else, that has converted evolutionary theory into a theory about genes rather than organisms. As we heard from one population geneticist, "The only mandatory attribute of the evolutionary process is a temporal change in allele [gene] frequencies".

There is little beyond quantifiable (digital or logical) entities in this picture — nothing material, plastic, and expressive, nothing qualitative, nothing through which the interior life of organisms can shine. We cannot connect anything in the particulate gene to our own conscious awareness, or to animal sentience, or to perceptual experience and cognition, or to the organizing ideas underlying animal form and behavior. If particulate genes account for these aspects of life, no one has a clue how it could be. Yet these genes are routinely posited as the evolutionary basis for understanding *all* life.

In the next chapter we will, finally, consider the fervent and influential defense of the "gene's-eye view of evolution" offered by Richard Dawkins.

Notes

1. For the record, currently relevant criticisms of genocentrism go all the way back a century. There is, for example, the brilliant work by marine biologist E. S. Russell, especially his 1930 book, *The Interpretation of Development and Heredity: A Study in Biological Method*, which I discussed in the previous chapter. In the modern era, one could start with *Exploding the Gene*

Myth by Harvard professor of biology Ruth Hubbard and Nobel Prize recipient Elijah Wald, or the essay, "Unraveling the DNA Myth", by cell biologist Barry Commoner.

The physicist, biologist, and philosopher of science, Evelyn Fox Keller, has illuminated genocentrism from many sides, including in her book, *The Century of the Gene*, published in 2000, and her chapter on Genes as Difference Makers in 2013. The one-time molecular biologist and now philosopher of science, Lenny Moss, wrote an incisive and influential critique titled *What Genes Can't Do* in 2003. And his book chapter, "Darwinism, Dualism, and Biological Agency" (2005), has perhaps never been exceeded for the succinctness and penetrating depth of its take-down of the controlling gene.

There are many other worthy commentaries on genocentrism, of which one (Gawne, McKenna, and Nijhout 2018) is cited below. See also Holdrege 1996, Rose 1998, Moczek 2012, Noble 2013, Walsh 2015, Noble 2018, and any number of other books and journal articles published over the past couple of decades.

Special mention also goes to University of Chicago microbiologist James Shapiro's book, *Evolution: A View from the 21st Century* (second edition, 2022). Evolution can only occur if there is useful variation, or potentials for variation, in the evolving organisms. And Shapiro provides overwhelming evidence that, whatever whole-organism features may count as viable heritable variation, organisms certainly have the genetic aspect very well covered. That is, they possess a sophisticated and wide-ranging ability to revise their own DNA — and they put it to use in a huge variety of ways. One could prefer that Shapiro not rely so heavily on computer and program metaphors, but nevertheless he makes abundantly clear the organism's effective exercise of a well-directed agency with respect to its DNA.

2. Disappointingly, those who continue giving support to genetic reductionism include proponents of the "extended evolutionary synthesis" and the "third way of evolution". As near as I can tell, these movements remain as thoroughly materialist in their fundamental assumptions as the evolutionary mainstream. It truly does appear that any questioning of the materialist dogma in biology is likely to spell the immediate end of an otherwise promising career. The existence of such metaphysical dogma in science ought to be ringing alarm bells on all sides.

3. For a discussion of the question of stability, see Chapter 22, "A Curiously Absolute Demand for Stable Variation".

4. Figure 21.1 credit: from Weiss 1971a.

5. Unconstrained supercoiling is supercoiling that creates tension. That is, in the unconstrained case the tension that results from supercoiling is not relieved by means of single-strand DNA breaks, the binding of proteins, or other means. I offer a very brief explanation of supercoiling in Chapter 3 ("What Brings Our Genome Alive?").

6. To speak of organizing ideas at work in an animal's life is not to imagine the animal *thinking them*. We will look at the distinction between an organism *possessing* its own intelligence and *being possessed by it* in our concluding chapter, "Some Principles of Biological Understanding".

7. Everything becomes nonsensical if we overlook or deny the inner power of the whole when in fact we have quietly transferred it to a part while pretending not to believe in it. Already in 1930

E. S. Russell recognized the consequences of this transfer:

> The germ-plasm, even in its modern genic form, is [thought to be] something which itself remains unaltered while acting as the cause of visible change in the organism. Aristotle would have recognized in this almost mystical conception something strangely like his “soul”! (Russell 1930, pp. 267-68).

I have no wish to belittle the idea of the soul. But anyone who believes in it should believe in it — not transfer it “under the table” to particular material particles, genetic or otherwise.

More recently the philosopher of biology Jason Scott Robert remarked on the “*animistic* (and otherwise problematic) idea of a genetic programme” (Robert 2004, p. 37). One of the most obvious ways DNA is treated as if it were by itself an animated, living being lies in the common, yet false, conviction that it exercises not only the powers of a human programmer in order to maintain and modify a single inherited “program” for the highly divergent purposes of hundreds of cell types (and trillions of cell contexts), but also the power to reproduce itself. In reality both the replication of DNA and its adaptation to the needs of different cell types are extraordinarily complex activities of whole living cells and organisms — activities of the sort we looked at throughout the first half of this book.

Sources

Barfield, Owen (1971). *What Coleridge Thought*. Middletown CT: Wesleyan University Press.

Burgess, Darren J. (2015). “Shaping Up Transcription Factor Binding”, *Nature Reviews Genetics* vol. 16, no. 259. doi:10.1038/nrg3944

Commoner, Barry (2002). “Unraveling the DNA Myth: The Spurious Foundation of Genetic Engineering”, *Harper’s Magazine* (February), pp. 39-47.

Dawkins, Richard (1995). *River Out of Eden: A Darwinian View of Life*. New York: BasicBooks.

Dawkins, Richard (2006). *The Blind Watchmaker*, third edition. New York: W. W. Norton. First edition published in 1986.

Gawne, Richard, Kenneth Z. McKenna, and H. Frederik Nijhout (2018). “Unmodern Synthesis: Developmental Hierarchies and the Origin of Phenotypes”, *Bioessays* vol. 40, no. 1, article 1600265. doi:10.1002/bies.201600265

Graur, Dan (2015). “Introduction to Molecular and Genome Evolution”. https://judgestarling.tumblr.com/post/129931383826/introduction-to-molecular-and-genome-evolution

Hartl, Daniel L. (1988). *A Primer of Population Genetics*, 2nd edition. Sunderland MA: Sinauer Associates.

Holdrege, Craig (1996). *Genetics and the Manipulation of Life: The Forgotten Factor of Context*. Hudson NY: Lindisfarne.

Hubbard, Ruth and Elijah Wald (1993). *Exploding the Gene Myth: How Genetic Information is Produced and Manipulated by Scientists, Physicians, Employers, Insurance Companies, Educators, and Law Enforcers*. Beacon Press, 1993.

Keller, Evelyn Fox (2000). *The Century of the Gene*. Cambridge MA: Harvard University Press.

Keller, Evelyn Fox (2013). “Genes as Difference Makers”, in *Genetic Explanations: Sense and Nonsense*, edited by Sheldon Krimsky and Jeremy Gruber. Cambridge MA: Harvard University Press, pp. 34-42.

Kurup, Jiji T., Ion J. Campeanu and Benjamin L. Kidder (2019). “Contribution of H3K4 Demethylase KDM5B to Nucleosome Organization in Embryonic Stem Cells Revealed by Micrococcal Nuclease

Sequencing", *Epigenetics & Chromatin* vol. 12, no. 20. doi:10.1186/s13072-019-0266-9

Lynch, Michael (2007a). "The Frailty of Adaptive Hypotheses for the Origins of Organismal Complexity", *PNAS* vol. 104, suppl. 1 (May 15), pp. 8597-604. doi:10.1073/pnas.0702207104

Lynch, Michael (2007b). *The Origins of Genome Architecture*. Sunderland MA: Sinauer Associates.

Moczek, Armin P. (2012). "The Nature of Nurture and the Future of Evodevo: Toward a Theory of Developmental Evolution", *Integrative and Comparative Biology* vol. 52, no. 1, pp. 108-19. doi:10.1093/icb/ics048

Moczek, Armin P. (2022). "When the End Modifies Its Means: The Origins of Novelty and the Evolution of Innovation", *Biological Journal of the Linnean Society* (July 6). https://doi.org/10.1093/biolinnean/blac061

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

Moss, Lenny (2005). "Darwinism, Dualism, and Biological Agency", in *Darwinism and Philosophy*, edited by Vittorio Hösle and Christian Illies. Notre Dame IN: University of Notre Dame Press, pp. 349-63.

Müller, Gerd B. (2019). "An Evolutionary Biology for the 21st Century", in *Perspectives on Evolutionary and Developmental Biology*, edited by Giuseppe Fusco. Padova, Italy: Padova University Press, pp. 29-39.

Noble, Denis (2013). "Physiology Is Rocking the Foundations of Evolutionary Biology", *Experimental Physiology* vol. 98.8, pp. 1235-43. doi:10.1113/expphysiol.2012.071134

Noble, Denis (2018). *Dance to the Tune of Life: Biological Relativity*. Cambridge UK: Cambridge University Press.

Robert, Jason Scott (2004). *Embryology, Epigenesis, and Evolution: Taking Development Seriously*. Cambridge UK: Cambridge University Press.

Rose, Steven (1998). *Lifelines: Life Beyond the Gene*. Oxford: Oxford University Press.

Russell, E. S. (1930). *The Interpretation of Development and Heredity: A Study in Biological Method*. Reprinted in 1972. Freeport NY: Books for Libraries Press.

Sachs, Joe (1995). *Aristotle's Physics: A Guided Study*. New Brunswick NJ: Rutgers University Press.

Sinden, Richard R. (2013). "The Helix Turns at 60: Writhing Free in Chromosomes", *Nature Structural and Molecular Biology* vol. 20, no. 3 (March), pp. 251-53. doi:10.1038/nsmb.2533

Walsh, Denis (2015). *Organisms, Agency, and Evolution*. Cambridge: Cambridge University Press.

Weiss, Paul A. (1971a). "The Basic Concept of Hierarchic Systems", in *Hierarchically Organized Systems in Theory and Practice*, edited by Paul A. Weiss, pp. 1-43. New York: Hafner.

Weiss, Paul (1971b). "One Plus One Does Not Equal Two", in *Within the Gates of Science and Beyond: Science in Its Cultural Commitments*, by Paul Weiss, pp. 213-61. New York: Hafner. Reprinted from *The Neurosciences: A Study Program*, edited by Gardner C. Quarton, Theodore Melnechuk and Francis O. Schmitt. Rockefeller University Press, 1967.

Chapter 22

A Curiously Absolute Demand for Stable Variation

There could hardly be a more frequently stated requirement for natural selection than this: *any beneficial genetic variation occurring in an organism, if it is to be evolutionarily relevant, must be stable, heritable, and long-lasting down through the generations.* If a given variation is likely to pass away after a generation or two, or if it quickly suffers further change, then the normally long and slow process of selection will not have time to spread the variation ("fix it") throughout a population. Patrick Bateson was giving voice to a universal consensus when he wrote, "For the Darwinian evolutionary mechanism to work, something must be inherited with fidelity" (Bateson 2017, p. 77).

But we might want to ask: If a certain amount of heritable stability is *in general* a requirement for evolutionary change, what is the counterbalancing principle that makes the *change* possible and is consistent with what we know of all organic processes of change? After all, every complex organism's development presents us with continuous and often intense transformation — including the kind of radical "melt-down" of old structures and subsequent "re-creation from scratch" we saw in the metamorphosis of the goliath beetle (Figure 17.1).

This near-total melt-down of the old form, followed by the emergence of a dramatically different form leads us to a second, equally important question: Is it certain material *products* of an organism's activity that must be stably maintained along a path of transformation? Or is it rather the contextual (holistic) *capacity for activity* — an activity through which not only do particular products arise, but also a coherent life is sustained and the character of a species (Chapter 20) is consistently expressed?

When the goliath beetle larva is overtaken by the seemingly chaotic "catastrophe" through which it will gloriously re-emerge in adult form, what is the organizing power, and what are the organizing ideas, through which this all-encompassing transformation of materials occurs? And how are the organizing ideas and power passed from one generation to the next?

(Is anyone writing Ph.D theses or journal articles or giving conference talks on such questions today? Would it even be allowed? Or has the materialist intellectual landscape of biology become a cowed and terrorized landscape — or simply an exhausted and dulled landscape?)

When we talk only about the inheritance of discrete *products* of activity, we have already shown a willingness to ignore the more fundamental problem of the origin of viable new *traits*, which require much more than some new bits of matter. Even if we are talking only about the development of the color patch (speculum) on a duck's wing feathers (Figure 11.2), we still need to embrace in thought a huge range of molecular interactions that are possible only as an expression of an integrated and living whole.

The obstacle to a proper reckoning with change and inheritance lies in the focus on isolated products that are seen primarily in relation to a specific molecule (DNA) and its genes — genes whose mathematically calculable spread through a population is then thought of as equivalent to the spread of traits, which in turn is taken to be evolution. It is the demand for this sort of sterile calculability that leads to a one-sided emphasis on stable variation (gene mutations) rather than on the potent activity of self-transformation that organisms put on such obvious display.

Such, I think we will see, is the heart of the matter. But we may get a fuller grip on the issues by starting with the popularly effective case Richard Dawkins has made for an avowedly particulate, "gene's-eye view" of evolution.

Richard Dawkins, genes and the biologist's "ultimate particles"

Richard Dawkins has been articulating his genocentric view of Darwinian evolution for over forty years, evoking, at the extremes, both passionate support and vitriolic criticism. Apart from the major controversies, however, there remains the oddity that the decisive failure of his view somehow rarely or never comes into clear focus, presumably because it is a defect found in virtually all conventional (and nearly all unconventional) thinking about evolution. I wish to pinpoint this failure as best I can.

In order for a genetic variation to be useful, Dawkins says over and over, it must be "potentially eternally heritable". "I'm not wedded to DNA", he assures us, but "I am wedded to this operational criterion that alterations in it go on forever potentially" (Dawkins 2009).

What he means is that, in order to be evolutionarily useful, variations must be *selected for* — perhaps not eternally, but at least for a long time. The ones that are harmful are selected *against*, and therefore tend to pass out of existence. But the truly beneficial adaptations can be selected and selected again, generation after generation, without any in-principle limitation. They are in this sense "potentially eternally heritable", which can only be the case if they are extremely stable.

The transgenerational longevity (stability) of genes is why Dawkins favors them, rather than whole organisms, as the true reproducers, or replicators, upon which natural selection works. "Bodies don't get passed down the generations; genes do" (Dawkins 2006b, p. 79). Just about all the details of one's body can change from one generation to the next. Bodies are, compared to genes, "like clouds in the sky or dust- storms in the desert. They are temporary aggregations or federations. They are not stable through evolutionary time" (Dawkins 2006a, p. 34).

For Dawkins, then, it is a non-repeatable collection of material bits, and not the character or the principles of organization at work in the body, that constitutes its identity. It is difficult to see how this amounts to much of an identity at all. But, in any case, such a mere aggregation can hardly be a significant evolutionary cause. "An individual organism is not [an evolutionarily relevant] replicator, because alterations in it are not passed on to subsequent generations" (Dawkins 1982). While an organism as a whole may be "the all important instrument of replicator preservation: it is *not* that which is preserved".[1]

No one, incidentally — neither Dawkins nor any other biologist — is saying that the organism's phenotype is irrelevant to evolution. Their claim is that the real relevance has to do with the fact that certain genes have contributed to this phenotype and therefore to the survival capabilities of the organism and its offspring. This in turn influences which genes will be passed down the line and survive in the larger population. It is, in this picture, the change (mainly the beneficial variation) in genes that most directly explains and maps to adaptive evolutionary change.

But beyond this question of the organism's survival, in which they themselves have a say, genes are thought to "live" independently of the particulars of an organism's life. They follow their own stable arc down through the generations, remaining just what they are except for the occasional chance mutation. They constitute, according to Dawkins, a nearly eternal "river of information". This river "passes through bodies and affects them, but it is not affected by them on its way through" (Dawkins 1995, p. 4).

Implied in all this — and very important for Dawkins — is the idea that genes can be conceived in something like a particulate fashion. "I insist on an atomistic view of [genes]", he wrote in *The Extended Phenotype* ("Dawkins 2008, p. 113). And elsewhere he has elaborated: "What I have done is to define a gene as a unit which, to a high degree, *approaches* the ideal of indivisible particulateness. A gene is not indivisible, but it is seldom divided. It is either definitely present or definitely absent in the body of any given individual. A gene travels intact from grandparent to grandchild, passing straight through the intermediate generation without being merged with other genes".[2]

Development versus Evolution

Dawkins is well aware that much of the criticism he has received comes from those studying the development of organisms. These observers find it very hard to recognize his genes in the developmental processes they investigate. It is, in many developmental contexts, impossible to assign genes long-lasting, discrete, well-identified causal roles, and also impossible to view genes as passing through these contexts unchanged in their functional significance for the developing and evolving organism.

In offering repeated responses to such criticism, Dawkins has made it clear that he considers the intricate choreography of development — in which many non-genetic factors figure prominently — to be irrelevant for evolution. But he emphatically rejects the charge that the gene-centered view denies "proper respect to the Great Nexus of complex causal factors interacting in development" (Dawkins 2008, p. 99). "I yield to no one", he told an Oxford debate audience, "in my admiration of the complexity of feedback loops, of the details — the immensely complicated details — whereby genes actually do influence phenotypes. There's absolutely no suggestion that it's irrevocably deterministic, there's absolutely no suggestion that it's simple" (Dawkins 2009).

And yet he fears that too many people get carried away by the intricacies of development. It is true, he grants, that it is precisely through development that we see how an organism grows and adapts toward maturity through complex and holistic processes. But these all too easily distract us from the decisive role of genes in evolution — a mistake he derisively equates to the lament, “Dear oh dear, development is a terribly complicated nexus, isn’t it?” (Dawkins 2004).

He himself prefers “frankly facing up to the fundamental genetic nature” of Darwinian selection (Dawkins 2008, p. 28). Development may be a “complicated nexus”, but evolution is merely a matter of pristine bits or bytes in an informational DNA sequence.

The fact just is, he says, that we learn nothing of interest by looking at the dynamic interrelations — the forming and dissolving, spaghetti-like causal arrows — through which DNA is fitted to its proper place among all the cellular activities. “There may be backwards arrows in all sorts of other senses but, in the sense that specifically matters for Darwinian evolution, the causal arrow of biological development from genotype to phenotype really is a one-way arrow” (Dawkins 2004).

The key to all this lies in two features of genes, as Dawkins sees them: (1) They can, through the occasional gene mutation, produce evolutionarily relevant variation in organisms. And (2) this genetic variation is characteristically stable; through the replication of DNA it can be passed down the generations potentially forever. This means that natural selection can, over as much time as necessary, change the distribution of genes in an evolving population. Very little other than genetic change, so the argument goes, yields particulate variation with such stability and lasting power and therefore little beside genetic change can contribute to evolution.

So, however vague and non-determinate genes may be for development, they are decisive for evolution. That’s why, for the evolutionist, “the complexity of development itself is an obscurantist red herring” (Dawkins 2004). Yes,

> development is terribly complicated, and we don’t yet understand much about how phenotypes are generated. But *that* they are generated, and *that* genes contribute significantly to their variation are incontrovertible facts, and those facts are all we need in order to make neo-Darwinism coherent (Dawkins 2008, p. 22).

And again:

> It doesn’t matter how complicated the developmental support structure, nor how utterly dependent DNA may be upon it, the central question remains: which elements ... of development have the property that *variations* in them are replicated, with the type of fidelity that potentially carries them through an indefinitely large number of evolutionary generations? (Dawkins 2004).

So it’s not just that genes qualify as drivers of evolution, but also that the other players in development do not. When we shift our attention from development to evolution, “the special status of genetic factors rather than non-genetic factors is deserved for one reason only: genetic factors replicate themselves, blemishes and all, but non-genetic factors do not” (Dawkins 2008, pp. 98-99). And, in perhaps his most succinct summary:

> The quality of hi-fi variation … is a precious, rare, onerous, difficult talent, possessed by genes and computer viruses and a few other things — but *genuinely* few … In order for anything to evolve by natural selection, there has to be variation in something that is both potentially long lasting and causally powerful, so that there emerges a difference, on the

> evolutionary time-scale, between the state of the world if one variant survives compared with the state of the world if an alternative variant survives. If neither variant survives more than a couple of generations anyway, we are not talking evolution at all (Dawkins 2004).

Genes, according to Dawkins, survive this rare and onerous test.

A short critique of Dawkins' view

Dawkins is admirably forthright about his desire for a purely genocentric explanation of evolution, and therefore also about his need to put evolution and development into different boxes. But it doesn't work. One thing both he and his critics could probably agree on is that development shows genes actually carrying out their biological roles. If we want to know what genes are and what they mean for the organism, then all the abstract talk in the world about "pristine bits and bytes" and "rivers of information" cannot supplant what we actually observe about genes in living contexts.

And this is where the problems begin. If Dawkins really is willing to concede the reality of the "Great Nexus of complex causal factors interacting in development" — if, that is, he recognizes the holism implied by the fact that the "causal arrows" of development run in all directions as guided by the larger context — then how can he turn around and say: "in the sense that specifically matters for Darwinian evolution, the causal arrow of biological development from genotype to phenotype really is a one-way arrow"?

Development, we can be sure, just is whatever it is, and it doesn't become different, right down into the nature of its causation, depending on whether we happen to be thinking about evolution at the moment. I can't believe he would argue with this, and I assume he would say his point is more subtle. But how that point might actually be put in a defensible way never clearly emerges. If genes accomplish their effects only in the context of tortuous interactions with innumerable constituents of the cell, then how do we avoid the conclusion that an evolution of these effects must require an evolution of the entire pattern of interactions?

I know: he would presumably say that cells, like bodies, are mere "clouds" or "dust storms", and couldn't possibly evolve. This is the strangest of arguments, but read on.

It does seem plain enough that Dawkins is saying *something like* the following, however he would like us to interpret it: while genes may not single-handedly shape the mature horse from a zygote, they do more or less single-handedly account for the transformation of the fox-sized horse ancestor, *Hyracotherium*, into the horse we know today (Chapter 19).

But consider: if the evolutionary re-shaping of animals such as *Hyracotherium* into the modern horse involves, as it must, a reorganization of the detailed, unthinkably intricate totality of developmental processes; and if genes are the lone, or almost the lone, factors accounting for this evolutionary reorganization, then I don't know how to avoid the conclusion that genes are the *causal, controlling masters of development generally*. And this suggests that Dawkins doesn't really accept the fact that multi-directional causal arrows are at work in the "Great Nexus of complex causal factors interacting in development". And if he doesn't accept this, it is presumably because he realizes that taking development at face value would torpedo his gene's-eye view of evolution.

My suspicion is that he simply never closely engages with the problems of development because he is uninterested in them and they are alien to his entire point of view.

In any case, the underlying problem is that the genes involved in complex developmental processes are not the genes Dawkins theorizes about. Think, for example, of the two key planks of Dawkins' argument and notice the distortion he introduces in each.

(1) Genes (Dawkins says) can, through the occasional mutation, produce evolutionarily relevant variation in organisms. The truth is, rather, that genes do not produce anything on their own. We have almost heard Dawkins himself say as much in the preceding paragraphs, where he mentions the unfathomed complexity of developmental processes and the "spaghetti-like" and "backward" causal arrows featured in them.[3]

Differences in cell traits always arise from the deeply interwoven activity of whole cells. In particular, the cell-to-cell variation along the path of a differentiating cellular lineage is a matter of the changing character of the entire cell as it participates in a transformative process leading to an endothelial cell in the inner lining of a blood vessel, or an amoeba-like macrophage devouring pathogens, or a crystalline, transparent cell of the eye's lens.

Yes, Dawkins claims to accept the "complicated nexus" of development. But where does he admit to, or even notice, the consistent, reliable, well-directed, holistic character of this development? A cell taking its place, along with its forebears and descendants, upon a coherent path of whole-cell change leading finally to a fully developed lens cell that must last a lifetime hardly shows the transience of a "dust storm in the desert".

Dawkins, of course, applies that phrase to entities involved in evolution, not development. But this is exactly the problem. The effort to separate evolution from development, as we will see shortly, does horrible violence to the most basic realities of inheritance upon which evolution depends.

Meanwhile, it is well to recognize the mystery we are up against in development. The differentiating cell acts as though it somehow "knows" where it is along the larger path of transformation. It "knows" how to use its inheritance from its parent cell not only to venture upon its own variation from that parent, but also to provide a distinctive inheritance for use by its daughter cell as material for still further variation — all this as a way each cell can participate in a coordinated movement toward an ultimate "goal" it can neither "see" nor consciously plan for. The cell participates, that is, in the intention or directiveness of its larger context, just as its constituent molecules participate in its own directiveness.

(2) Genetic variation is "potentially immortal" (Dawkins 2008, p. 83) **— stably holding to its own identity and remaining unchanged by the organisms hosting it down through the generations**.[4] This is another radical distortion of the truth. A whole cell may indeed be potentially immortal in Dawkins' sense, something well-known by biologists who have, in laboratory dishes, cultured single "cell lines" derived from a single cell — and have kept these cell lines going for several decades with no apparent limitation in sight. Actually, all life on earth is commonly thought to be the flourishing, down through countless generations and in countless different species, of the life of a single original cell of unknown origin.

But if cells are potentially immortal in some sense, genes — in the causal sense that Dawkins fixates upon — certainly are not. In fact, their causal powers do not even remain constant in a single cell over its lifetime. This is because local activity within the cell is always being coordinated and repurposed according to the needs and interests of the whole cell and organism.

Dawkins gets his river of fixed, unchanging, selectable "particles" of inheritance only through an act of intellectual violence — only by mentally wrenching certain molecular parts of DNA (for example, the nucleotide bases constituting the genetic "code") from their meaningful, dynamic chromosomal and cellular contexts. He abstracts them from the stream of life in which alone they become what they are moment by moment. He wants dead, material things for theoretical manipulation. You might say that he abstracts the genetic "letters" from the cellular "sentences" in which they find their life and meaning.

Only such an act of abstraction can give him what he needs: heritable particles to which he can apply the same name (even if not the same meaning) from one context to the next — particles that can be tracked within both individual organisms and breeding populations. Then, because the name of any particular gene remains the same, he can pretend he is always talking about precisely the same, unchanging thing.

And yet we know very well that, in the living and meaningful sense, genes never remain unaltered for long. The "same" genes can have radically different causal implications in different contexts within a single cell or organism, and also in different kinds of cell or organism. Even when we think a gene has analogous functions in different organisms, it can turn out that the functions have unrecognizably different physiological realizations. This reflects the very different ways of being from one kind of organism to another — ways of being in which genes are caught up rather than being the decisive orchestrating factors.

As one of endless evolutionary examples: the PAX6 gene is found in both fruit flies and mammals, and has been thought of as a "master control gene" for the formation of eyes. But not only is its activity now known to be interwoven and interdependent with that of countless other genes and their regulating factors and functions, but the compound eyes of a fruit fly are altogether different organs compared to the eyes of a mammal. If we try to imagine a gene, *as a single, supposedly well-defined causal unit*, independent from the stream of life in which it finds itself and yet at the same time fitting itself into the completely different physiological contexts of fly and mammal, the picturing does not go well.

Throughout the first half of this book we have seen over and over how DNA is caught up in, and given its functional identity by, its context. And in Chapter 21, I illustrated some of the countless ways in which the DNA content of genes is itself twisted, untwisted, bent, distorted in various ways, chemically modified, moved around in the nucleus, converted to nonstandard double-helical forms or even non-double-helical forms, and otherwise driven by the cell into conditions that transform its genetic role and identity.

And so, we have now seen that it is the principle of holism that subverts both premises of Dawkins' argument. (1) Genes may be among the conditions for cellular (and organismal) variation, but they do not produce that variation; the whole cell (or organism) does. (2) Genes, considered as important causal factors in evolution, are not "potentially immortal" — or even potentially "lifetime-lasting" within individual organisms — because the whole organism defines and redefines their nature and identity as it goes through its life-long processes of development.

To put the matter in these terms, however, would doubtless provoke Dawkins' skepticism. For he has very publicly worried that "a kind of 'holistier than thou' self-righteousness has become fashionable", and further, "There are times when holistic preaching becomes an easy substitute for thought, and I believe the dispute about units of selection [genes, in his view] provides examples of this" (Dawkins 2008).

But when it comes to understanding the life of organisms, holism is just about the most disastrous thing to lose sight of.

The embodied organism is not like a cloud

I have just now been contending that if there are lower-level, "potentially immortal", directive, and agential entities within organisms, then they are whole cells, not genes.[5] But what I have said about cells applies all the more to organisms (which Dawkins identifies with "bodies").

Recall Dawkins' claim that bodies are like clouds or dust storms in the desert because they do not exhibit the constancy required for natural selection and evolution. But this fantasy of the whole organism's transitory existence — its lack of a stable and enduring identity — is as wildly off the mark as his invention of the "almost eternally" durable genetic particle.

It is true that, much like a differentiating cellular lineage, a multicellular organism as a whole undergoes continual change. It is alive. In its development, it grows from a zygote to a mature form. This is a drama of progressive self-manifestation or self-realization, a drama of reliable, continuous transformation, where no material structures (including chromosomal structures) remain always the same. It's what organic activity always is: if an organism, along with all its parts, is not changing in a well-directed and holistic manner, it is dead.

But well-directed development no more represents change without stable identity than does cell differentiation. If a differentiating cell "knows" very well who it is and where it is going, all the more a developing organism follows a reliably defined path of development and self-expression leading to its own fullest realization. Crucially, this path is never *precisely* defined or *materially* determined. For example, adjustments to unpredictable environmental disturbances during development may continually occur. But the adjustments are *in the service of* the organism's fullest expression of its true nature.

The identity here is that of a *dynamic* unity. But a dynamic unity capable of maintaining itself while actively participating in and vulnerable to its context is a far more profound center of identity and power than a supposedly static particle impervious to its surroundings.

Never, except in the imagination of someone preferring to live within a world of inert (but nicely stable) particles, could the organism have been likened to a cloud or dust storm. Its unity and stability lies in its giving material expression to a specific *kind* or *species* (Chapter 20). Every complex organism is an almost miraculous, stable, reigning unity governing many differentiating cell lineages (over 250 in the human case). The reliability and constancy of this sort of identity is so evident that for millennia nearly everyone erroneously assumed that all species were eternally fixed in their essential nature.[6]

In order to correct this view today, we do not need to throw out the constancy everyone can observe, but only to render the idea of that constancy more dynamic in line with modern evolutionary insights. An organism's identity is crucially reflected in its ability to adapt to a changing environment in line with its own species-character and potentials. We see this dynamic identity and adaptability even in individual organisms, and also in our own biographies. Our immediate experience gives no support to the idea that growth, development, and change imply a lack of coherent identity.

To observe life, then, is always to watch an interplay of change within continuity, plasticity within constancy. Both aspects of the living interplay run through all biology. Perhaps our most convenient access to them comes through the study of development, as when we watch a whole organism "coming to itself", or watch a differentiating cellular lineage.

Here the principle of change is easy enough to verify — and it no more relies on the absolute constancy of the material products of change than does the metamorphosis of the goliath beetle larva into a mature beetle (Box 17.1). I described in Chapter 17 how hundreds of cell lineages in our bodies "evolve" (are differentiated), not by remaining mostly unchanged, but rather by compounding change upon change down through the cellular generations. The result is a profound, qualitative transformation of whole cells, explainable only as a power of activity, not as a determination by previous material constituents.

It is difficult to doubt that this compounding of change upon change is owing to an orchestrating power that works throughout the entire cell — a power not at all one-sidedly determined by genes, their mutations, or any other material constituent of the cell. We are watching a cell radically re-organize itself in its entirety.

But think what this means. If many developmental changes in a cell lineage are not stable and heritable over any large number of cellular generations, it is because *they had better not be*. After all, the lineage is *on the way to somewhere*, proceeding directionally along a pathway of integral, holistic transformation. This suggests how differently we will have to look at evolutionary processes once we are willing to acknowledge the nature of organic change and a directive agency.

There is no need to avert our eyes from the "dangerous fluidity" of the whole situation. For the other aspect of the process of cell differentiation lies in the fact that the differentiating cellular lineage is remarkably sure of its identity: it is *this* lineage, and is powerfully "insistent", in tune with its context, about reaching *its own* mature character. And, having reached its maturity, it is capable of stably maintaining it as long as necessary, while never losing a degree of adaptability.[7]

So here in the organism's development and cellular differentiation, we see compelling identities involving, not the stasis of inert particles, but rather a marriage of constancy and change, selfhood and transformation — a reality it would be very strange for any student of evolution to lose sight of.[8] What is constant is not a mere physical product, but an active way of being. As I have put it a number of times (drawing on a phrasing of the Greek scholar, Joe Sachs), an organism is "continually at work remaining itself". We could say much the same of a cell. Physical entities — aggregations of particles, if we insist against all reason in thinking that way — are the inconstant residue of such activity, not a cause of it.

A decisive counter-picture to the gene's-eye view of evolution

The central problem that Dawkins avoids reckoning with is this: everything we have noticed about the enduring unity, purposiveness, and transformational powers of the cell and organism applies, not merely to development, but also directly to evolution. That's because

> *what passes hereditarily between generations is never less than a whole cell, and this whole cell is never less than a whole organism. And, as we have seen, both the cell and the organism exhibit an enduring, purposive identity possessing not only constancy, but also a profound transformative capacity — exactly the combination an evolutionary theorist must look for.*

Anyone who wants to claim that genes, rather than whole living cells (organisms) are the basis for evolution needs to explain why we must ignore everything we know about cells — about how they proceed so effectively along evolutionary (developmental) trajectories and how they intricately, flexibly, and authoritatively enlist their genes along with all their other resources in achieving their ends.

Further, why should we assume that the totipotent zygote (capable of engendering all the cell lineages of the adult organism) brings nothing of its self-transformative, re-organizing powers *across the generational gap* — nothing, that is, of evolutionary relevance? There is, of course, really no gap at all, but only continuous life. And the activity of whole-cell transformation is fully as insistent on the parental side — in the unique differentiation of germ cells and the seemingly against-all-odds merging of distinct germ cells with distinct genomes in a single zygote — as it is on the offspring side.

We know a great deal about the powers of reliable change possessed by cells and organisms, and we also know about a gene's complete inability to represent on its own an organism's expressive traits. If it happens (as it does) that an organism's abilities as a living, developing, striving-to-survive "vehicle" for its genetic cargo require all its vast array of transformational powers, and if we see it employing those powers with almost infinite intricacy and adaptational effectiveness in all its cell lineages, why should we imagine these powers going dead or inert at those especially intense moments when one generation is actively preparing for a successor generation.

One can only assume that Dawkins has proven blind to the only agents of biological transformation we know because, as a materialist and reductionist, he simply cannot tolerate the idea of biological agency, despite what he witnesses in every organism he has ever seen. He *must* overlook active and purposive organic wholes by conceiving organisms as built, bottom-up, from collections of inert particles and mindless processes. But, as I have pointed out repeatedly in this book, such a conception is never possible to hold consistently, and all observation-based biological description immediately controverts it. (See, for example, Chapter 2.)

The organism's dynamic, transformative capacities are so clearly underwritten by everyday perception that they need not even be mentioned in order to be casually, if also silently, relied on by the evolutionist. But when the failure to mention them turns into an active "conspiracy of silence", so that our theories of evolution must ignore the obvious, then something has gone badly wrong.

WHERE ARE WE NOW?

Sterile Particles, or Living Cells?

It would hardly be surprising to suggest that a great deal of one's evolutionary theorizing depends on whether one approaches the topic with the mindset of a materialist and reductionist or, to the contrary, ascribes to every cell and every organism a wise agency and purposiveness expressed in all its living activity. But before tackling that issue directly, one can always begin by looking at what we know of cells.

This chapter is grounded in a seemingly incontrovertible fact observed in all complex organisms: their cells proceed through dramatic processes of differentiation reflecting organizing ideas in which the entire cell is caught up and through which it undergoes profound transformation. Cells can, to all appearances, become as different from each other as any two organisms with dramatically different genomes. But the differences between cell lineages in a single organism cannot, in any fundamental sense, be attributed to genetic differences, because all the lineages derive from a single, inherited genome.

The question this poses for evolution is straightforward — and puzzlingly ignored on all sides: Why should this transformational capacity of whole cells be ignored as a source of evolutionary change — ignored, that is, when we shift our view toward the cell-organism that in undisputed fact bears the full inheritance passing between generations? It's true that the question is a difficult one because the kind of dramatic, qualitative, whole-cell transformation we encounter so often in developmental studies cannot be reduced to mathematically analyzable changes in gene sequences and gene frequencies. But why wouldn't we expect *any* explanation for the evolutionary transformation of an organism to be at least as complex as the organisms themselves? This complexity of holistic processes is certainly no reason to turn away from their investigation when we are seeking to understand evolution.

Notes

1. Dawkins 2008, p. 114. Dawkins is quoting himself from an earlier paper in *Zeitschrift für Tierpsychologie*.

2. Dawkins 2006a, pp. 33-4. Along these same lines, Dawkins has written that the “digitalness [of genes] is probably a necessary precondition for Darwinism itself to work” (Dawkins 2006b, p. 163). I discuss this remark along with the non-digital character of genes in Chapter 21, “Inheritance, Genetics, and the Particulate View of Life”.

I would add here that my criticism of Dawkins’ “atomistic” genetic particles is in no way intended to deny the fact that genes, like much else in the organism, possess their own *particularity*. Just as an enzyme has an affinity for a particular substrate or substrates, so also a gene is associated with its own suite of protein variants. The cell flexibly employs the gene as a resource for the generation of one or another of those variants. The cell, of course, requires many other resources for this task, and the decisive, repeated modification of a protein over its lifetime is achieved *after* the gene-resource has been brought into play for the initial synthesis of the protein.

3. It is similarly false when Dawkins says that genes “replicate themselves”. They are utterly helpless to replicate themselves — and also to perform error correction on themselves. It is the cell that both replicates them and carries out DNA damage repair. (He surely does understand this, despite his language.) On the power of proteins to manage DNA and reassemble shattered DNA, see Chapter 8.

4. More specifically, it is genetic variation *in the germline* that Dawkins says is potentially immortal.

5. It is important to realize that DNA with its genes must also have a share in the cell’s character inasmuch as it can *participate in, or be caught up in*, the well-directed purposiveness of the cell. But DNA is not itself the *responsible center or mediating agent* for that purposiveness, which belongs to the larger context. We are, as always when dealing with organisms, looking at an organic relationship between part and whole, and between wholes nested within larger wholes.

6. It is this *kind* that, as we saw in Chapter 20, the usual genetic studies cannot approach. For these studies unavoidably focus on trait differences between closely related organisms, and the differences found are then correlated with gene differences. So one is studying no more than inessential changes among organisms of the same general type and is gaining little or no insight into the determinants of different types. (We should note that Dawkins’ genetic preoccupations are based precisely on the results of such studies, with their limited applicability to evolution.) The limitations of genetic studies are rooted in the fact that genetic crosses between organisms of substantially different types are as a rule non-viable.

7. It would be good not to forget what we learned in Chapter 6 about cells changing their “identity” in the hair follicle niche, depending on circumstances. We have to understand the cell’s identity in a broad enough way to recognize this possibility of metamorphosis. It illustrates

how cells are subordinate to, and receive their identity from, the larger context and the organism as a whole.

8. Change and continuity: every organic whole embodies — lives by means of — a harmonization of these contrasting principles. But these are exactly the principles that any theory of evolution must somehow hold together. It's obvious enough that you can't have evolution without change. But so, too, without continuity there is only the arbitrary substitution of some elements of a mere aggregate for others, with nothing that lends significance to the result. If the change is to be non-arbitrary or coherent, there must be a persistent character attributable to the whole. Without an underlying continuity no enduring, nameable entity or being exists of which we can meaningfully say, "Yes, *this* is evolving". There is instead just "one damn thing after another".

And we should add this: if, as in the organism, *all* the material elements are subject to change, then the underlying continuity must be immaterial (Barfield 1965, p. 96). But then, that is how we have understood the organism all throughout this book — as a bodily exterior "shone through" by an interior.

Sources

Barfield, Owen (1965). *Unancestral Voice.* Middletown CT: Wesleyan University Press.

Bateson, Patrick (2017). *Behaviour, Development and Evolution*. Cambridge UK: Open Book Publishers.

Dawkins, Richard (1982). "Replicators and Vehicles" in *Current Problems in Sociobiology*, edited by King's College Sociobiology Group, pp. 45-64. Cambridge: Cambridge University Press.

Dawkins, Richard (1995). *River Out of Eden: A Darwinian View of Life*. New York: BasicBooks.

Dawkins, Richard (2003). "An Early Flowering of Genetics", *The Guardian* (February 8). https://www.theguardian.com/books/2003/feb/08/peopleinscience.evolution

Dawkins, Richard (2004). "Extended Phenotype — But Not *Too* Extended. A Reply to Laland, Turner and Jablonka", *Biology and Philosophy* vol. 19, pp. 377-96.

Dawkins, Richard (2006a). *The Selfish Gene*. Oxford: Oxford University Press. Originally published in 1976.

Dawkins, Richard (2006b). *The Blind Watchmaker*, third edition. New York: W. W. Norton. First edition published in 1986.

Dawkins, Richard (2008). *The Extended Phenotype*, revised edition (1999), reprinted with corrections (2008). Oxford: Oxford University Press. Original edition published in 1982.

Dawkins, Richard (2009). Comments during "Homage to Darwin" debate, Balliol College, Oxford University (May 8), featuring Richard Dawkins, Lynn Margulis, Steve Bell, and Martin Brasier. The event was chaired by Oxford's Denis Noble. Links to recordings of all three parts of the event can be found at http://www.voicesfromoxfordorg/?s=homage+to+darwin . (Downloaded December 5, 2022.)

Chapter 23

The Evolution of Consciousness

“The economic and social structure of Switzerland”, wrote Owen Barfield in his major work on the evolution of consciousness, is owing in part to the tourist industry, which in turn depends upon the fact that “the *mountains* which twentieth-century man sees are not the mountains which eighteenth-century man saw” (Barfield 1965, pp. 145-46).

Barfield is gesturing toward an evolution of consciousness that, as he saw it, implied an evolution of phenomena. Taken literally (as indeed he intended it), his claim easily baffles even serious attempts to fathom it. Most observers will conclude that the claim is either outrageous or else trivially expresses the idea that, while our *experience* of the mountains has changed, the mountains themselves have certainly not. But the question of the relation between reality on one hand and our experience of reality on the other is subtle and potentially disorienting for us today. It is also inseparable from the troubled, several-hundred-year quest for an empirical (experience-based) science of the objective world. Does “experience-based” mean science is inescapably subjective, or instead that our experience bears the marks of an objective reality?

In this chapter we will use Barfield’s remark as little more than a stimulus to begin looking at the evolution of consciousness. By the time we are done, however, the question about the relation between human experience and the world we so naturally think of as wholly objective and mind-independent may have gained a more intriguing aspect. But we will forego until the next chapter any effort to throw light on the underlying issues. These have to do with the way we are situated in the world through our cognitive experience.

We now begin by looking at a few aspects of the evolution of language.[1]

There was a primordial unity of inner and outer meaning

According to the evolutionary story that most of us have forcibly absorbed through our education, humankind somehow raised itself above the beastly, mindless, material substrate of its origin so as to achieve, step by step, the mystifying wonders of language and poetry, music and art, politics and science, and all the other sublimations contributing to high culture. The sea of meaning within which we now swim — without which we would have nothing we could recognize as human life — *somehow* bubbled up from *somewhere*, if only as an illusion of the human mind, and cast a kind of spell over the bedrock meaninglessness of brute matter.

“Somehow”, I say, since the meaning at issue and the question how it could have emerged from an eternal silence of Unmeaning is so great an enigma for conventional thinking that it has received no fundamental elucidation.

What is not enigmatic — and is clearly available to investigation — is the fact that when we look further and further back through history, we see an ever richer language, not an increasingly material and "de-meaned" language reflecting our supposedly brutish origins. As the nineteenth-century English poet Percy Bysshe Shelley observed, "In the infancy of society every author is necessarily a poet, because language itself is poetry" (Shelley 1840).

We do not, that is, discover ancient literature to be impoverished relative to modern literature. It is more like the reverse of this: we still debate today whether, for example, the Homeric epics — composed orally before the development of writing in ancient Greece — have ever been surpassed for psychological depth, dramatic power, poetic subtlety, and human interest.

We will take the philologist and historian, Owen Barfield, as our primary guide, first, to the evolution of language, and then to the evolution of consciousness more generally. Barfield devoted a long life spanning the entire twentieth century to the study of these two topics, and about the former he wrote:

> "The farther back language as a whole is traced, the more poetical and animated do its sources appear, until it seems at last to dissolve into a kind of mist of myth. The beneficence or malignance — what may be called the soul-qualities — of natural phenomena, such as clouds or plants or animals, make a more vivid impression at this time than their outer shapes and appearances. Words themselves are felt to be alive and to exert a magical influence" (Barfield 1967, pp. 87-88).

The "enchanted" landscape of ancient consciousness, as Barfield sketches it for example in *Poetic Diction*, could not have been one of conscious invention, unrestrained metaphor, or causal speculation. The earliest historical evidence shows us that humans were not yet possessed of the sort of selves, or the resources of language, conducing to such invention and hypothesis. They simply observed nature as it was given to them. Their meanings did not arise from anything like modern reflection or theorizing, but were encountered directly, as if spoken by the earth itself.

This truth has been disguised from us by what Barfield referred to as "logomorphism" — the projection of modern thought processes onto "that luckless dustbin" of the primitive mind. "The remoter ancestors of Homer, we are given to understand, observing that it was darker in winter than in summer, immediately decided that there must be some 'cause' for this 'phenomenon', and had no difficulty in tossing off the 'theory' of, say, Demeter and Persephone, to account for it" (Barfield 1973, pp. 74, 90).

But we are given no evidence that the mythic mind had any concern with such explanations, if only because the conditions for them did not yet exist. Our modern ideas of cause and effect lay far in the future. The ancient fact of the matter was more like this: "In the myth of Demeter the ideas of waking and sleeping, of summer and winter, of life and death, of mortality and immortality are all lost in one pervasive meaning" (Barfield 1973, pp. 90-91).

Think for a moment about what we mean today by "explaining the world". Such explanation requires two distinct awarenesses: that of something "out there" posing a puzzle for us, and an understanding "in here" that clarifies the puzzle. But our ancestors did not possess these separate awarenesses. Unlike us, they were not in a position to dualize the world into outer material fact and interior explanatory idea. They lacked the requisite psychological distance from the world, and therefore did not experience the otherness of “things” as we do. The mythically enchanted landscape was, for them, an unanalyzed interfusion of outer and inner, of sense perceptions and soul content.

For example, the story of the Greek sun-god “Helios” could hardly have originated as an animistic effort to account for a material sun, given that neither the history of language nor what we can surmise of mythic consciousness affords any evidence that a purely material sun had yet been conceived. The sun’s glory, its light and warmth, were directly and non-reflectively experienced as ensouled realities.

We still find remnants of such indivisible meaning in later eras, as when we read in the *New Testament*,

> Truly, truly I say to you, unless one is born of water and the spirit, he cannot enter into the kingdom of God … The wind blows where it wishes and you hear the sound of it, but do not know where it comes from and where it is going; so is everyone who is born of the spirit. (John 3:5-8)[2]

Translators into English have been forced to use two different words, “spirit” and “wind” (in other texts “breath” is required) where the original Greek has a single word, *pneuma*. “We must, therefore, imagine a time”, Barfield noted, “when [Latin] ‘spiritus’ or [Greek] ‘pneuma’, or older words from which these had descended, meant neither *breath*, nor *wind*, nor *spirit*, nor yet all three of these things, but when they simply had *their own old peculiar meaning*, which has since, in the course of the evolution of consciousness, crystallized into the three meanings specified”[3] (Barfield 1973, pp. 79-81).

“Nor yet all three of these things” — not the addition of one distinct meaning to another, but a single unity encompassing wind, breath, and spirit. The distinct meanings had not yet arisen, and so were not available to be added together. Our current dualism of “inner” and “outer” was not yet part of human experience. It is hard for us to appreciate this at a time when our language forces a dichotomous choice between the terms of outward, sensible reference and those drawn from our interior life.

We will take one further example, this one drawn from Barfield’s *History in English Words*:

> As far back as we can trace them, the Sanskrit word “dyaus”, the Greek “zeus” (accusative “dia”), and the Teutonic “tiu” were all used in contexts where we should use the word *sky*; but the same words were also used to mean *God*, the Supreme Being, the Father of all the other gods … If we are to judge from language, we must assume that when our earliest ancestors looked up to the blue vault they felt that they saw not merely a place, whether heavenly or earthly, but the bodily vesture, as it were, of a living Being (Barfield 1967, pp. 88-89).

Summing up the historical picture, the nineteenth-century American transcendentalist, Ralph Waldo Emerson, wrote in his 1836 book, *Nature*: “As we go back in history, language becomes more picturesque, until its infancy, when it is all poetry; or all spiritual facts are represented by natural symbols”. And again: “It is not words only that are emblematic; it is things which are emblematic”[4] (Emerson 1836, pp. 33, 37).

Figure 23.1. Egyptian sky goddess, Nut, and earth god, Geb, held apart by Shu, a god associated with air and wind.

So the direction of the evolution of language and meaning is, so far as we can discern from the historical record, the opposite of an "ascent from brute materiality". Before humans could speak in their individuated voices, or could even conceive of devising theories about nature, the natural world spoke to and through them — meaningfully and poetically. The rhythm and meter we find, for example, in the epic Homeric hexameters with their "thundering epithets" were, Barfield wrote, relics of a time "when men were conscious, not merely in their heads, but in the beating of their hearts and the pulsing of their blood — when thinking was not merely *of* Nature, but was Nature herself" (Barfield 1973, pp. 146-47).

Looking back upon myths such as that of Demeter and Persephone (where *you and I* are likely to see metaphor or simile) Francis Bacon pointed out the error of this view: "Neither are these only similitudes, as men of narrow observation may conceive them to be, but the same foot-steps of nature, treading or printing upon several subjects or matters".[5] And regarding these "footsteps of nature", Barfield adds:

> Men do not *invent* those mysterious relations between separate external objects, and between objects and feelings or ideas ... The language of primitive men reports [these footsteps] as direct perceptual experience. The speaker has observed a unity, and is not therefore himself conscious of *relation*. But we, in the development of consciousness, have lost the power to see this [unity] as one (Barfield 1973, pp. 86-87).

What words can teach us about the evolution of consciousness

There is one province of reality, one domain of the material world, where we humans have gained a knowledge unexcelled in its sophistication, its fine detail, and its almost infinite nuance of meaning. It is a domain that, perhaps more than any other, shapes our lives and influences our happiness day in and day out. And knowledge of events within this domain comes naturally: nearly all humans achieve a level of expertise dwarfing the scientific researcher's mastery of material phenomena in all other disciplines.

The phenomena I am referring to are those coming to expression in the human face. I have specifically in mind, not the power of producing those expressions, but rather of objectively reading them. For, of course, we do read them objectively. Our lives and society would be impossible if we could not navigate the universe of facial gestures with a largely shared understanding. *This* means *that*. The face illustrates how, in physical features, we are dealing with meaning borne upon a material dynamic of force and substance, but not explicable as if the meaning arose from, or were *caused by*, that dynamic. We naturally think of the cause as operating in some sense *interior* to its outer manifestation.

And what we have seen in the preceding section is that the face of nature herself presented our ancestors with a countenance whose inner significances were inseparable from what we today would consider its outer manifestation. Natural phenomena constituted a living language, rather as, still for us today, the sense-perceptible human face can at times scarcely be distinguished from its expressive eloquence — from the meaning it communicates.

The history of language gives us ample evidence pointing back to the kind of inner/outer unity we are presented with in the Greek *pneuma*. Barfield shows how we can see this in two broad classes of words:

Nearly all those words now bearing immaterial meaning in the form of high abstraction, or else referring to our interior life, were once inseparable from sensible experience.

Emerson was not the first to recognize this truth when he wrote in 1836:

> Every word which is used to express a moral or intellectual fact, if traced to its root, is found to be borrowed from material appearance. *Right* means *straight; wrong* means *twisted*. *Spirit* primarily means *wind; transgression*, the *crossing of a line; supercilious* the *raising of the eyebrows* … *thought* and *emotion* are words borrowed from sensible things, and now appropriated to spiritual nature (Emerson 1836, chapter 4).

The idea is not that the interior or psychic aspect was lacking in the perception of ancient folk, but rather that it was bound together inseparably with the outer, material meaning. And, as Barfield reminded us, this truth extends far beyond words like *spirit*, *thought*, and *emotion*:

> To what, precisely, does each one of them refer — the tens of thousands of abstract nouns which daily fill the columns of our newspapers, the debating chambers of our legislatures, the consulting rooms of our psychiatrists? *Progress*, *tendency*, *culture*, *democracy*, *liberality*, *inhibition*, *motivation*, *responsibility* — there was a time when each of them, either itself or its progenitor in another tongue, was a vehicle referring to the concrete world of sensuous experience with a tenor [immaterial meaning] of some sort peeping, or breathing, or bursting through (Barfield 1977, p. 38).

Moreover, as Barfield stresses, high-sounding scientific terms “are not miraculously exempt” from the general rule. A great part of the explanatory apparatus of science consists of largely abstract and dematerialized words such as *stimulus*, *cause*, *effect*, *reference*, *control*, *repress*, *information*, *code*, and *program*, all of which can be shown to have been once inseparable from an “outer clothing”. Only with time did the abstract or inner meanings become detached from sense perception. By abstracting away from that clothing we gained the powers of thought necessary for our current science[6] (Barfield 1973, p. 134).

The other group of words, now referring to material, sense-perceptible phenomena, once also connoted sentience or inwardness.

We have already seen how ancient words for “sky” also meant “divine being”. The very words by which we today designate the materiality of the world are sufficient to make the point. “Matter” likely traces back to Latin *mater*, “mother”. And “physical” derives from Greek *phyein*, “grow”. So the Greek *ta physika* — “natural things” or “things of external nature” — was rooted in living activity. Of course, as we also noted earlier, words by which we now refer to purely physical bodies such as “sun”, “Venus”, “Mars”, “Jupiter”, and “Saturn” can be traced back to the names of various deities.

So words now having a purely immaterial significance once also referred to sensible phenomena, and words now purely sensible or material in reference once also referred to interior experience. Taken together, these two groups of words testify to the primeval experience of nature as a material/immaterial, outer/inner unity before the dualization of this unity in the modern sense was even conceivable.

But none of this is to say we should look to etymology for current meanings. Will anyone claim today that when we say someone is “wrong”, we really mean he is bent like a stick, or that to “conceive” something is to grasp it physically? The dualization of the world *has* occurred, and one result is that we now enjoy a vast panoply of meanings and a diverse range of distinctions formerly unavailable. Nevertheless, the history of meaning raises its own questions.

How could the unitary meanings of our ancestors have possessed their primordial, immaterial aspects if the associated, sense-based images (a bent stick, the hand’s grasp) were not inherently expressive of an immaterial reality?[7] If the indissoluble unity of sensible image and immaterial meaning were arbitrarily invented by early speakers and were not inherent in the phenomena themselves — if things were not, as we heard from Emerson, essentially *emblematic*, but were instead subject to any speaker’s arbitrary, metaphoric invention — how would others have picked up on the speaker’s invented, immaterial meanings? Indeed, how could the very possibility of immaterial meanings ever have come about, if the original reality out of which humans emerged was (what we think of today as) solely physical?

The cognitive experience of the ancients was *given* by nature. Its inner, expressive content was not added by a reflective or theorizing perceiver, but was already experienced in perception. Things meant something *on their face*. Our ancestors were, you might say, participant-observers entranced by an ensouled drama staged within their own consciousness by the world’s phenomena.[8]

What the historical record shows is that those ancestors recognized, in whatever was expressed through natural phenomena, a speaking agency akin to themselves. “Whether it is called ‘mana’”, wrote Barfield, “or by the names of many gods and demons, or God the Father, or the spirit world, it is of the same nature as the perceiving self, inasmuch as it is not mechanical or accidental, but psychic and voluntary” (Barfield 1965, p. 42).

Today our evolutionary trajectory has brought us to a vastly different place — a place where we are routinely taught to think disparagingly of the ancients as astonishingly naïve. But whatever our thoughts and meanings may be, we ought to acknowledge with some humility that they are available to us only because the world first mimed them, so to speak, thereby enabling them to light up in human minds “naïve” enough to read the face of nature in a way that few of us today can.

At the same time, we will need to acknowledge that, so far as the historical record testifies, our evolutionary trajectory has not accorded with the usual assumptions. There is no evidence that we slowly ascended from a crude life of material unmeaning to a humanly and artificially contrived realm of meaning, value, culture, and spirituality. Our life today, with its materialistic convictions and experience of a meaningless world, has required a long descent from the living, ensouled landscape upon which our ancestors were nurtured.

Our evolutionary heritage, culminating in Cartesian dualism, has taught us to insist upon a radical separation of the inner and outer dimensions of our experience, which once formed so compelling a unity. And then, under the further influence of materialist thought, we have learned to regard the inner dimension as “merely subjective” or somehow less than fully real.

But perhaps, instead of projecting our current mental processes upon the “woefully subjective and ignorant” ancients, we might want to consider how our own history may have cut us off from an ancient wisdom, finally concreting in our deepest, most unyielding, and largely unconscious habits of thought and experience. Through such reflection, perhaps we would gain the freedom within ourselves to inquire in all seriousness whether we today are the ones who lack ready access to much of the world’s reality.

All this suggests how advisable it might be for us to take a closer look at the evolution of consciousness through which our own thinking has gained (and become limited by) its current character.

Europeans and their changing landscape

In his book on *The Changing Nature of Man*, the Dutch historical psychologist Jan Hendrik van den Berg described the dawning among Europeans of something like our modern “sense of nature”. This emerging sense, he claimed, can be recognized in Jean-Jacques Rousseau’s *Confessions*, where he describes a trip through the Alps in 1728. It came to full expression in his novel, *Julie, or the New Heloise* (1761). With surprising rapidity for such a fundamental historical change, the new appreciation of nature took Europe by storm:

> Like an epidemic the new sensation spread through Europe. Every one wished to see what Rousseau had seen, to experience the same ecstasy. Everybody visited Switzerland and climbed the Alps. This had not happened before Rousseau. It was then that the Alps became a tourist attraction. Previously they had been an obstacle .... Even in 1750, Henault, a poet and a friend of Voltaire’s, crossed the Jura and the Alps without the least enthusiasm, merely observing, “There is always a creek at my side and rocks above my head, which seem about to fall in the creek or upon me.” These words would nowadays disqualify him as a poet (van den Berg 1961, p. 233).

Figure 23.2. A photo of the Alps taken from above the town of Flims in the Imboden Region in the Swiss canton of Graubünden.[9]

If there was an “epidemic” of sightseeing, it was not caused by Rousseau’s published descriptions. Rather, his descriptions were themselves an early symptom of the epidemic.

Before commenting on Rousseau, van den Berg had mentioned Da Vinci’s Mona Lisa. People came from far and wide to see this painting because it was, as van den Berg put it, “the face of later generations”, the revelation of a new way to live. Mona Lisa was smiling over the delicious and unexpected discovery of an interior secret, a hidden subjectivity, powerful enough to remake the world. The sudden flowering of the Renaissance, the childlike fervor of the Scientific Revolution, the compelling urge that sent Magellan and the other great voyagers steadfastly beyond the edges of the world, where sea monsters once dwelt — all testified to a humanity *waking up* from its medieval enchantment. We stretched, blinked, rubbed our eyes, looked out upon a fresh world we were seeing for the first time. And, in that moment, we became aware of the one who was inside, looking.

A subject becomes a subject by virtue of its ability to stand apart — to stand within itself — and make whatever is now "out there" an object for itself. A new subjectivity is necessarily married to a new objectivity. So it was not only Mona Lisa's smile that became famous, but also the landscape behind her. We must see her smile and its interior significance against that external backdrop. Van den Berg saw it as

> the first landscape painted as a landscape, just because it was a landscape. A pure landscape, not just a backdrop for human actions: nature, nature as the middle ages did not know it, an exterior nature closed within itself and self-sufficient, an exterior from which the human element has, in principle, been removed entirely (van den Berg 1961, pp. 231-2).

Van den Berg proceeds to quote Rilke: "This landscape is not … the judgment of a man on things at rest; it is nature coming into being, the world coming into existence, unknown to man as the jungle of an unknown island. It had been necessary to see the landscape in this way, far and strange, remote … It had to be almost hostile in its exalted indifference, if, with its objects, it was to give a new meaning to our existence"[11] (van den Berg, pp. 230-31).

So, what was going on with the changing relation between Europeans and their landscape? Were people just "talked into" seeing the Alps differently, or was a deeper, underlying change at work? Were our forebears several centuries ago becoming situated in their environment in a fundamentally different way? Did Da Vinci, foresighted as he was in so many ways, catch a first, premonitory glimpse of nature detaching herself from the human being — a strange sight at first? And did Rousseau testify to the historical transition toward a comfortable, aesthetic *appreciation* of this new reality?

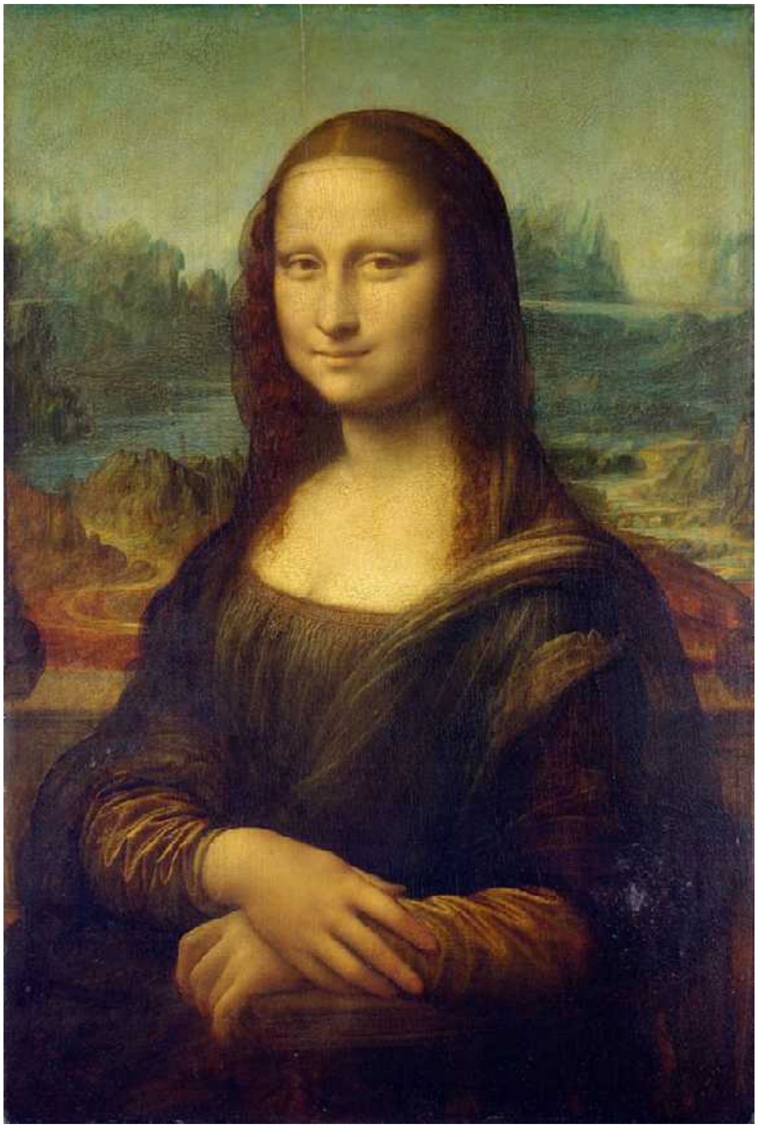

Figure 23.3. Leonardo Da Vinci's "Mona Lisa".[10]

History of ideas — or an evolution of consciousness

A familiar task for any philosopher or historian would be to trace the impact, say, of Aristotle's or Descartes' or Darwin's thought upon subsequent thinkers. We think of it as a history of ideas. But what if there are changes of consciousness that run mostly along subterranean channels of which we have no immediate awareness? After all, we might well wonder how we got from the undivided, inner/outer (neither subjective nor objective) consciousness inherited from the age of myth to our own detached-observer subjectivity today, where we find ourselves confronted by "mindless natural objects".

A fundamental premise of Barfield's work was that there is a crucial distinction to be made between the history of ideas and the evolution of consciousness: "A history of thought, as such, amounts to a dialectical or syllogistic process, the thoughts of one age arising discursively out of, challenging, and modifying the thoughts and discoveries of the previous one" (Barfield 1965, p. 67). This is, for example, the way the history of philosophy is normally taught.

On the other hand, any method for approaching the evolution of consciousness must be quite different. What matters is not so much *what* people are thinking as *how* they are thinking, and how they are connected, in the greatest depths of their being, to what is happening in the world, both material and immaterial. Intellectual thoughts or theories about this or that are less relevant to the evolution of consciousness than the unconsidered habits of thought and the qualities of experience determining what they *can* think.

We need to notice, in particular, qualities of *meaning*. To focus on "propositional content", as we think of it today, is to make the ancients into objects of ridicule by assuming that they were engaged in something like our own detached, self-aware habits of intellectual debate. We mistake their immediate *perceptions* for our own philosophically loaded *thoughts*, and so we discover in the ancients only confusion.

It was to evolutionary studies that Barfield continually returned as he illustrated, in a series of works spanning several decades, how the meanings of words "are flashing, iridescent shapes like flames — ever-flickering vestiges of the slowly evolving consciousness beneath them" (Barfield 1973, p. 75). He tried to show that the processes of evolution, while not determining the particular ideas of a given era, do circumscribe the kinds of things one can conceive and mean.[12]

As an example, the historian Herbert Butterfield describes how the Aristotelian worldview gave way during the sixteenth and seventeenth centuries:

> Through changes in the habitual use of words, certain things in the natural philosophy of Aristotle had now acquired a coarsened meaning or were actually misunderstood. It may not be easy to say why such a thing should have happened, but men unconsciously betray the fact that a certain Aristotelian thesis simply has no meaning for them any longer — they just cannot think of the stars and heavenly bodies as things without weight even when the

> book tells them to do so. Francis Bacon seems unable to say anything except that it is obvious that these heavenly bodies have weight, like any other kind of matter which we meet in our experience.

Butterfield adds that there was, during this period, “an intellectual transition which involves somewhere or other a change in men’s feeling for matter” (Butterfield 1957, pp. 130-31). Sometimes, as other historians have noticed, certain thoughts just seem to be “in the air”. For whatever reason, their time has come.

Barfield suggests that even the history of ideas, when looked at closely, can reveal “forces at work beneath the threshold of argument”. Using the linguist’s term “Aryan” in something like the modern sense of “Indo-European”, he notes that “the comparatively sudden appearance, after millennia of static civilizations of the oriental type, of the people or the impulse which eventually flowered in the cultures of the Aryan nations can hardly have been due to the impact of notion on notion. And the same is true of the abrupt emergence at a certain point in history of vociferously speculative thought among the Greeks”.

And still more remarkable, he says, is the “historically unfathered impulse of the Jewish nation to set about eliminating participation”. By “participation” (see following section) he refers to the ancient sense of a numinous presence in nature that was akin to the human interior. And so,

> Suddenly, and as it were without warning, we are confronted by a fierce and warlike nation, for whom it is a paramount moral obligation to refrain from the participatory heathen cults by which they were surrounded on all sides; for whom moreover precisely that moral obligation is conceived as the very foundation of the race, the very marrow of its being. We owe to the Jews the pejorative significance in the word *idol*. The representative images, the totemic *eidola*, which ritually focused the participation of the surrounding Gentile nations, are either condemned by their prophets as evil or denied as unrealities …” (Barfield 1965, pp. 67-68).

It is good to realize how, even in studying relatively recent history (or the cultural realities of our own day), we are always looking at more than a discursive play of ideas. We may indeed be focused on the history of ideas, but there is always a deeper current to be aware of. In a moment we will glance at earlier stages in the evolution of consciousness. But, first, we will draw from Barfield one further example illustrating how even the usual historical narratives can suggest something about an underlying evolution of consciousness.

Speaking of the introspective psychology that yielded the theories of Freud and Jung, Barfield refers to the “startling phenomenon” whereby “a literal-minded generation developed a sympathetic response to the psycho-analytical gnosis of dream-imagery, and accepted the (one would have thought) fantastic idea of an immaterial realm of ‘the unconscious’”. Who, he wonders, could possibly have foreseen this, say, in the year of the Great Exhibition (1851)?

The question is meant to voice our inevitable puzzlement if we look merely at an intellectual history, tracing the impact of idea upon idea. For, in intellectual terms, the second half of the nineteenth century represented the zenith of that literal-mindedness exemplified by a science recognizing, at bottom, only the mindless and deterministic interaction of atom with atom. Whatever sort of change yielded the possibility of psychoanalysis was not the mere product of the discursive play of extant ideas, but rather of the changing (evolving) structure of human experience.

And so, leaving aside the question of the long-term significance of psychoanalysis, Barfield remarks that “for the historian of consciousness the most significant thing will always be the way it ‘caught on’; the number of its technical terms — and still more the characters out of Greek mythology — which had become household words even before the death of its founder. Pan, it seems, has not only not retired from business; he has not only gone indoors; he has hardly shut the door, before we begin to hear him moving about inside”[13] (Barfield 1965, pp. 133-34).

The long historical arc of the evolution of consciousness

Barfield devoted much of his life to tracing the evolution of consciousness, so far as the historical record — and especially the record of language use in western civilization — can reveal it. He schematized this evolution in the form of a ‘U’, where the left leg marks a long descent from mythic “original participation” to detachment, following which we might hope for a (still to be achieved) re-ascent toward what he called “final participation”.

The detachment, which western civilization has been experiencing with particular intensity for the past several hundred years, involves disconnection from a material world that now seems wholly “out there” and independent of the human interior. But the important flip side of this independence is the birth of the self-possessed and more or less free human individual. It is this individual who, without giving up her independence, can enter into “final participation” by reconnecting with the world’s interior through love and consciously directed cognition and activity.

Original participation was a kind of unfree or instinctive inner union with the world — a union we saw reflected in the words of ancient languages. Our ancestors were relatively un*self*-aware, yet conscious of an intimate, interior connection to what lives in the world. Or perhaps we should say: they themselves simply *lived* in and through this interior connection. Their experience was collective rather than highly individualized or private.

Crucially (as I already noted above in the discussion of the history of language), theirs was a time when the meaning of things was directly given to the human being from the world — when, as Barfield observed, “thinking [was] at the same time perceiving”. Without a detached and individuated self-consciousness to question it, experience just was what it was. There could have been no philosophers or scientific researchers.

To have our thoughts given to us directly along with our perceptions (rather than our having the responsibility to enliven perceived contents at least in part with thinking we experience as “our own”) would have been a condition we can scarcely imagine today. There was, in the most remote era we can glimpse through the literate, historical record, “a picture-thinking, a figurative, or imaginative consciousness, which we can only grasp today by true analogy with the imagery of our poets, and, to some extent, with our own dreams" (Barfield 1973, pp. 206-7).

We have come a long way from that original participation. (Only a very late stage of the journey was indicated in the changing relation to the landscape briefly discussed above.) But the freedom we have thereby gained is not unproblematic. Disconnection from the world in which we live is a kind of death. It amounts to being severed from the sources of our own life, as reflected in the widespread feeling that we live in a meaningless world. The freedom of detachment easily loses all content — we can find no more reason to do *this* than to do *that* — and therefore freedom can become mere emptiness. The question is whether we can employ our freedom and independence in order to reconnect with the spiritual sources of our lives.

It is important to realize the change in directionality here. In the unfree state of original participation we were gaining from the world a language that could eventually serve for our *selves* — we were, you might way, *being spoken* into being, thereby gaining the potential to become the modern selves that we are. To move forward now, however, requires us freely to participate in the creative processes by which the world itself first served us: we must play our own part in *speaking the world* into the coming phases of its existence. This is the reversal of direction — the movement from the left leg of the evolutionary 'U' upward into the right leg.

We are not lacking stimulus for pursuing this movement. Our current era of detachment presents us with a picture of centrifugal forces threatening society with disintegration. Former institutions, traditional values, and blood ties become ever weaker factors in holding societies together, leaving many with a kind of vertigo suggesting that everything is falling apart. This in turn may produce a backlash in the form of various defenses of an "old order" that no longer holds promise of helping us along our way to the future.

Perhaps we see signs of that future in the way our present situation has called forth not only burgeoning volunteer activities from free individuals, but also flourishing non-governmental organizations across the political spectrum and a growing sense of individual and social responsibility — responsibility for local and global environments (including social and political environments), for the protection of all forms of life, and for the fruitful direction of evolution itself. The change I spoke of a moment ago — between *being spoken* on one hand and *speaking* on the other — marks nothing less than a critical transformation of the very agency of evolution, which is inevitably falling more and more to our own conscious choices.

An ideal degree of detachment — before and after

If Mona Lisa hinted at a new, more private and individuated sense of the human interior, and if, correlative to this detachment of the human being, there was a dawning sense of a landscape that was "pulling away", gaining its own independent existence so that it could begin to be noticed as such, then we might wonder where this change was coming from, and where it might be going — or where we, in our current state, might help to direct it.

Here is one way to contextualize these particular changes. If, along the way from original participation toward near-total disconnection from the world, there is a certain ideal aesthetic distance, a point of maximum fascination, a mutual interplay of subject and object wherein humans and their world resonate in the most exquisite tension, then, Barfield maintained, it was the Romantics (1770-1870) who lived closest to that condition. It was the point where humans had become sufficiently detached from the world to notice and appreciate the independent life of “things”, but not so detached that they lost all consciousness of their inner connection to them. Their separation from the world only allowed them to savor all the more their resonance with it.

This was the state being entered by those who, as we heard above, first rushed out to see the mountain vistas and to revel in what became known as “picturesque”[14] scenes of nature. The distancing process, however, was not arrested or reversed by the Romantics, so that van den Berg is correct in observing how “the estrangement of things, which brought Romanticism to ecstasy, belongs, for the most part, to the past.” We are no longer close enough to the world even to feel the conscious fascination of our estrangement. Today,

> Many of the people who, on their traditional trip to the Alps, ecstatically gaze at the snow on the mountain tops and at the azure of the transparent distance, do so out of a sense of duty. They are only imitating Rousseau; they are simulating an emotion which they do not actually feel. It is simply not permissible to sigh at the vision of the great views and to wonder, for everyone to hear, whether it was really worth the trouble. And yet the question would be fully justified; all one has to do is see the sweating and sunburned crowd, after it has streamed out of the train or the bus, plunge with resignation into the recommended beauty of the landscape to know that for a great many the trouble is greater than the enjoyment (van den Berg 1961, p. 233).

Which one of us doesn’t feel at least some symptoms of this detachment from nature? But perhaps, in order to contextualize a little more fully the changes running from the Renaissance of Da Vinci through the Romanticism of Coleridge and Goethe to the alienation of our own day, it will be useful to add a picture from the period immediately preceding the Renaissance. Here is Barfield trying, in just a few words, to give an impression of the qualities of medieval consciousness — a consciousness still possessing more than a few echoes of original participation:

> If it is daytime, we see the air filled with light proceeding from a living sun, rather as our own flesh is filled with blood proceeding from a living heart. If it is night-time, we do not merely see a plain, homogeneous vault pricked with separate points of light, but a regional, qualitative sky, from which first of all the different sections of the great zodiacal belt, and secondly the planets and the moon (each of which is embedded in its own revolving crystal sphere) are raying down their complex influences upon the earth, its metals, its plants, its animals and its men and women, including ourselves … Our own health and temperament are joined by invisible threads to these heavenly bodies we are looking at …
>
> We turn our eyes on the sea — and at once we are aware that we are looking at one of the four elements, of which all things on earth are composed, including our own bodies. We take it for granted that these elements have invisible constituents, for, as to that part of them which is incorporated in our own bodies, we experience them inwardly as the “four

> humors" which go to make up our temperament. (Today we still catch the lingering echo of this participation, when Shakespeare makes Mark Antony say of Brutus:
>
> > *… The elements*
> > *So mixed in him, that Nature might stand up*
> > *And say to all the world, This was a man.)*
>
> … A stone falls to the ground — we see it seeking the center of the earth, moved by something much more like desire than what we today call gravity … (Barfield 1965, pp. 76-77).

From myth to literacy: the coming into focus of the human individual

The earliest "histories" of which we can catch a glimpse were not centered on human events. Indeed, the idea of distinctively *human* events can hardly have been available. The accounts were more like spiritual and cosmic histories. Humans — their gaze riveted by fascinating goings-on in what we today might denigrate as "supernatural" realms, but which they experienced (pre-reflectively) simply as *nature* — did not narrate their own histories. Rather, as is still echoed in Hesiod's *Theogony* long after the primary age of myth, they told stories of the genesis of gods and nature spirits. Only with time would history become more human-centered and prosaic.

We saw earlier in this chapter how the most ancient historical evidences and the linguistic shards that remain of mythical experience suggest a language, a manner of consciousness, and an experienced world, very different from our own. There existed a unity of the "inner" and "outer" dimensions of experience that has almost wholly disappeared from our modern engagement with the world, strongly polarized as the latter is between self and other, subject and object. What we know today as the "material world" was then alive or "enchanted", and humans were aware that in the world they met powers akin to, even if other than, their own power of directed activity. So, too, what we know today as the "inner world" was then embodied, inseparable from sense-perceptible expression.

The trajectory from the age of original participation to the present has been a long one, and — apart from some hints (derived from language) about the mythic consciousness — we have looked only at a few relatively recent "snapshots". It is time to get some sense for the larger picture.

At the edge of literacy and beyond

Between the age of myth and the medieval era, there lay the long period beginning (at different times in different places) with the earliest forms of literacy. In Greece, the Homeric epics, first in oral form and then in writing, straddled the beginnings of literacy. In those epics we find “meaning still suffused with myth, and nature all alive in the thinking of man”:

> The gods are never far below the surface of Homer’s language — hence its unearthly sublimity. They are the springs of action and stand in place of what we think of as personal qualities. Agamemnon is warned of Zeus in a dream, Telemachus, instead of “plucking up courage”, meets the goddess Athene and walks with her into the midst of the hostile suitors, and the whole earth buds into blossom, as Zeus is mingled with Hera on the nuptial couch … And these august beings, speaking now from the mouths of the characters, and again passing and repassing invisible among them, dissolve into a sort of *largior aether* [greater, or transcendent, sky], which the Homeric heroes breathe all day; so that we, too, breathe it in the language they speak — in their ῥοδοδάκτυλοσ ἠώσ [“rosy-fingered dawn”], their ἱερὸν ’ἦμαρ [“sacred day”], in the sinewy strength of those thundering epithets which, for all their conventionality, never fail to impart life and warmth to the lines (Barfield 1973, pp. 93-94).

Following Homer something like a miracle occurred within Greek culture. In his widely used textbook, *The Story of Art*, the eminent art historian, E. H. Gombrich, refers to the “Great Awakening” that took place in Greece from the seventh through the fifth centuries B.C.E. (Gombrich 1989, chapter 3). Painters and sculptors began to do more than follow the rather schematic rules of representation handed down through the centuries, but also observed for themselves, and tried to be faithful to their observations.

Figure 23.4. Top portion of a large Greek funerary vase ("krater") with a prothesis scene — presentation of the deceased’s body on a table. The vase originated around 750–735 BCE. Note the geometric decorative patterns on the vase, and the “geometrically” repeated human figures.[15]

The older style is shown in Figure 23.4. It is hard for us to appreciate the strange forms given to the human figures on this vase — forms in what has become known as the “geometric style". Surely, we might well think, Greek eyes were as capable of physically registering the actual form of the human body as ours are. But apparently — and so various authorities have argued — Greeks before and during the Homeric era experienced their bodies rather differently from us. The classicist Bruno Snell described how the art gives the impression that "the physical body of man was comprehended, not as a unit but as an aggregate" (Snell 1960, p. 6). Or, as Mark Vernon puts it, the Greeks of this period must have experienced their bodies "rather as baggy gatherings of spirited factions", not as well-integrated entities.

Vernon is a theological scholar and psychotherapist who has traced the evolution of consciousness down through both Greek and Jewish cultures. Describing the geometrically styled human figures as having "bull-like thighs, wasp-like waists, barrel-like chests, pin-like heads", he goes on to say that the "locus of aliveness wasn't set within a person's frame and physique … Instead, their identity came from the outside in, with different limbs and organs attuned to external divine influences. The inner life of the cosmos was their inner life". Further, he says,

> They had little or no notion of the isolated individual … and little sense of a unified self who was or could hope to be in charge. To be alive, to be functioning, was implicitly tied up with being porous to society, spirits, gods. [On the vases] the people appear to move as one, as if swaying in a field of consciousness like as many wheat ears blown by the wind" (Vernon 2019, pp. 47-49).

Figure 23.5. Greek (Attic) Panathenaic prize amphora. The painter employed the black-figure technique to depict runners in a race. From about 530 BCE.[16]

Figure 23.6. Ancient Greek bronze statue of a youth, from the Antikythera shipwreck. The statue dates to circa 340-330 BCE.[17]

But by degrees with the beginning of the Great Awakening, the figures begin to gain individual and personal traits (Figures 23.5 and 23.6), while at the same time the artist takes up a personal point of view, and perspectival foreshortening starts to come into play. Correlative with this, Athenian democracy took form, refecting an individualizing mindset. In the case of the fifth-century sculptor, Pheidias,

> His figures weren't generic presences with blank eyes. They looked at you. They conveyed a sense of alertness and interiority ... His works were immediately recognized as spell-

> binding, displaying a dignity and beauty that called forth an interiority from within the viewer … His work was instrumental in showing a clear image of the integrated person, thereby spreading a sense of it in others … The best sculptures could now show the interactions of individuals. They left behind the collective swaying of the masses (Vernon 2019, pp. 50-51).

In 1953 Snell published an influential book called *The Discovery of the Mind*. It contained discussion not only of the intimate relation between the Homeric heroes and the speaking of the gods, but also traced in the tragedians (Aeschylus, Sophocles, and Euripides) a movement from the centrality of fate to that of the individual conscience. And he described how “the early Greek lyrists had awoken to the fact that man has a *soul*; they were the first to discover certain features in the feelings of men which distinguished those feelings sharply from the functions of the physical organs”. Further,

> For the first time it was noticed that these feelings do not represent the intercession of a deity or some other similar reaction, but that they are a very personal matter, something that each individual experiences in his own peculiar fashion, and that originates from no other source but his own person. Further they had found out that different men may be united with one another through their feelings, that a number of separate people may harbour the same emotions, memories, or opinions. And finally they discovered that a feeling may be divided against itself, distraught with an internal tension; and this led to the notion that the soul has intensity, and a dimension of its own, viz. depth (Snell 1960, p. 301).

The Great Awakening was a time when the individual human thinking activity was vigorously detaching itself from perception and gaining a sense of its own free powers. Barfield, referring to the work of the Greek philosophers, particularly Aristotle, wrote:

> Struggling to fit herself as into a glove, to the processes of cause and effect observed in physical phenomena, the mind became suddenly conscious of her own shape. She was astonished and delighted. She had discovered *logic* (Barfield 1967, p. 109).

Turning toward the Jewish scriptures and culture, to which Vernon brought his theological training: he recalls, for example, how the Jewish prophets urged the people toward monotheism — toward acknowledgment of a God whose name was I AM. This was inseparable from an awakening of the individual worshipper. Only someone who was becoming an individual in his own right could “perceive the singularity of the divine nature”. “A felt sense of ‘I am’, even if transient, is a prerequisite for feeling the inner power of the divine I AM”. As Barfield summarized it, the locus of participation was narrowed down to the divine name, which Jews could hardly speak without invoking their own inwardness (Barfield 1965, p. 155). Thereafter,

> Nature can be experienced as [the] speaking of God rather than itself being divine, enchanted and haunted, and God can speak through creation but not be held within creation … Henceforth, monotheistic knowledge of God would be inextricably tied up with self-knowledge, and introspection would become a key spiritual task (Vernon 2019, pp. 36-41).

Under Hezekiah (the king of Judah who reigned from the later eighth into the early seventh centuries BCE), a general literacy was encouraged for the first time. The individual worshipper could now read the sacred texts for herself and ruminate over them internally. Old idols and sacred groves were banished, and clan tombs were replaced with burial sites for single families or individuals. All these developments, Vernon points out, were associated with a transition from collective religious ritual and experience to the importance of the emerging life of the ethically responsible and self-aware individual.

But the path from original participation through detachment and then toward reconnection of our now-independent consciousness with the spirit in the world that gave birth to us is not easy. The vigorous philosophical speculations and disciplines of the Greeks would eventually be frozen into the mathematical, rule-bound, one-sidedly cause-and-effect mindset of modern science — a kind of wooden materialism from which we have yet to find any decisive exit.

So, too, the growing Jewish awareness of individual moral responsibility would eventually (during the centuries leading up to the destruction of the temple in Jerusalem in 70 CE) be paralyzed under the weight of external laws and a prescriptive literalism that left little room for creative individual insight into the moral potentials inhering in every situation. Still today, in various religious fundamentalisms, we find the same tendency.

The evolution of consciousness, like all evolution, is not a straight line

As the preceding two paragraphs indicate, the evolution of consciousness has been far from a smooth, linear progression. As civilizations have risen and fallen, so too there have been periods of rapid advance toward new forms of consciousness, attempted returns to a more “paradisal” consciousness, and various sideways movements.

Consider, for example, the development of the art of visual perspective in the Renaissance. This reflected and powerfully contributed further to the development of individual points of view, while also supporting an individual and quantitative experience of space where previously there had been something more like a collective space of meaning:

> Before the scientific revolution the world was more like a garment men wore about them than a stage on which they moved. In such a world the convention of perspective was unnecessary. To such a world other conventions of visual reproduction, such as the nimbus and the halo, were as appropriate as to ours they are not. It was as if the observers were themselves *in* the picture (Barfield 1965, pp. 94-95).

And yet, dramatic and important as the late-medieval and Renaissance discovery and embrace of perspective proved to be, it was not altogether new. This is why it has been referred to as a “rediscovery” (White 1972). There was in antiquity — in Greek and Roman culture — a genuine anticipation, in theory and practice, of linear perspective. It was lost in subsequent centuries, but when the time was right, was rediscovered and flourished during the Renaissance in a way that took permanent hold and changed everything.[18]

Similarly, we find during the Hellenistic era that managing one’s own subjectivity, or soul life, became a central problem addressed by Epicurean and Stoic philosophers. But here again the movement into this particular sort of self-awareness and concern for “care of the soul”, did not lead directly to the dramatic emergence of the modern individual that we have witnessed since the Renaissance and Scientific Revolution.

We began this chapter with Barfield's comments about how the mountains of Switzerland we see today are not the same mountains our ancestors saw. Of course, in today's environment the nearly universal assumption will be that Barfield was not really talking about the mountains themselves, but "only" about how people see and experience the mountains. And we did learn above how different this experience became during the transition from medieval to modern culture.

Actually, however, Barfield really *was* talking about the mountains themselves, whose reality he did not believe could be radically or dualistically distinguished from our experience of them. His refusal to treat the distinction between reality and experience as fundamental reflects a long-running conviction within science that our knowledge of the world must be empirically based — rooted in experience. Our knowledge of the world is always a thoughtful clarification within our own minds of the thought and sense inherent in the world we experience, and we need not pretend that this clarification takes us beyond the experienced world or is anything other than a thoughtful elucidation of experience.

I did say at the outset that I was not about to attempt an explanation of Barfield's deeper meaning in this chapter. And I will hold to that. But I do hope that the preceding notes on the evolution of consciousness may at least make his mysterious suggestion about the Swiss mountains more intriguing — and may also fortify the reader for the perhaps unexpected challenges to contemporary thinking in Chapter 24. That chapter offers, among other things, a possible approach to Barfield's meaning.

WHERE ARE WE NOW?

We've come a long way

Here is some of the ground we have covered in this chapter:

♦ The ancients, who were incapable of anything like our own theoretical and causal speculation, directly perceived a world that seemed to possess a powerful interior aspect. They recognized what lived in the world as akin to what lived in their own interiors.

♦ Our ancestors' thoughts were at first *perceived* more than actively *thought*. Their meanings and language were given in their immediate perceptions of the world around them. Eventually, an independent inner being and independent powers of speech arose as a further, inward development of what had initially been the world's "speaking".

◆ Historically, there has been a change in directionality. We humans who were, in a sense, first spoken into being by the world, now find ourselves bearing a responsibility to speak this world's future into being — if only, to begin with, by accepting a responsibility to avoid destroying it.

◆ Our lately achieved independence from the world as self-aware individuals has given us the freedom to think and imagine the world with our own thoughts, even if in a highly distorted way. We are free to err. We are free to "forget" humanity's origin and past, if only by ignoring the study of it. We can, if we wish, retreat into a comfortable materialism requiring no burden of responsibility on our part.

The chapter as a whole concerns *human* consciousness, but the picture certainly suggests that *all* organisms make their way through a larger, meaning-soaked surround that comprises the givenness of their lives and the givenness of the world. And it is this same meaning that, by contracting into a bright focus in human minds, has engendered our consciousness and self-awareness. In this common, if diverse, interior aspect lies the unity of life on earth.

Our discussion of the evolution of consciousness does not suggest that it makes any sense to imagine an *origin* of consciousness. More particularly, it is not clear how the idea of a "first" meaning arising from bedrock meaninglessness can make sense. We cannot grasp any meaning except against a contextual background full of already existing meaning. Make an experiment: take any single word (or invent one) and try to understand or define it other than in the terms of many other words. You will find that any specific meaning can shine forth only in the light of a meaning-soaked universe.

The background of meaning is simply a given of our lives as children of what we might call a *logos*-world. We cannot even legitimately imagine an origin for meaning, because the only contents available to our thought-world are meaningful contents. An imagined leap from unmeaning to meaning can occur only via circular reasoning, whereby elements of meaning are brought in through the back door.

In short, there can be no meaninglessness in the *known* universe — in a universe that submits itself to human perception and understanding. For a more explicit treatment of these matters, see Chapter 24.

We have learned to view just about everything through an evolutionary lens. The benefits to understanding have been many. The oddity is that these benefits have scarcely been extended to a knowledge of the evolution of consciousness — an evolution that includes the changing cognitive relation between the perceiver and what he perceives. There is a penalty to be paid for this: we lose the ability to understand the very different qualities of consciousness characteristic of earlier eras, and therefore we become trapped in modernity — in our own "moment" of evolution. And this at a time when we need to begin learning to carry responsibility, not just for one moment, but for the entire future course of evolution.

Notes

1. The next two sections are adapted from Talbott 2018.

2. The translation is from the New American Standard Bible.

3. Barfield also tells us that “such a purely material content as ‘wind’, on the one hand, and on the other, such a purely abstract content as ‘the principle of life within man or animal’ are both *late* arrivals in human consciousness. Their abstractness and their simplicity are alike evidence of long ages of intellectual evolution. So far from the psychic meaning of [latin] ‘spiritus’ having arisen because someone had the abstract idea, ‘principle of life …’ and wanted a word for it, the abstract idea, ‘principle of life’ is itself a *product* of the old concrete *meaning* ‘spiritus’, which contained within itself the germs of both later significations” (Barfield 1973, pp. 80-81).

4. Actually, words were inseparable from things. For the ancients, a word and its reference were not distinct things. This begins to make sense when one realizes (as we will see more clearly below) that the human being did not yet have a private or subjective interior where he could become aware of words as his own property set over against an objective world wholly other than himself.

5. From Bacon’s *Advancement of Learning*, II.v.3., quoted (and translated) in Barfield 1973, p. 86.

6. Might it be that the necessity for this “dematerialized” language of science tells us something about the power of science to deliver a strictly material understanding of the world?

7. For a treatment of this and related questions, see Barfield’s essay, “The Meaning of ‘Literal’” in *The Rediscovery of Meaning and Other Essays*, pp. 32-43. Perhaps equally valuable is his essay on “The Nature of Meaning”.

8. Barfield would say we must also come to terms with the reverse truth: the phenomena are themselves an evolving, ensouled drama staged in the “outer” world by conscious beings. That is, consciousness and the phenomena (whose objective nature is to occur within consciousness) are correlative. But this radical notion would take us far beyond the current exposition. For some related discussion, see Chapter 24.

9. Figure 23.2 credit: Zacharie Grossen, CC BY-SA 4.0.

10. Figure 23.3 credit: public domain photograph of the painting in the Louvre, available here. The image has been digitally lightened to counter darkening that has resulted from aging.

11. The foregoing paragraphs are drawn directly from my chapter, “Mona Lisa’s Smile” (Chapter 21) in Talbott 1995.

12. Barfield, a philologist whose approach to the evolution of consciousness was primarily through the study of words, wrote that the evolution of consciousness requires us “to penetrate into the very texture and activity of thought, rather than to collate conclusions. It is concerned, semantically, with the way in which words are used rather than with the product of discourse.

Expressed in terms of logic, its business is more with the proposition than with the syllogism and more with the term than with the proposition” (Barfield 1965, pp. 67, 90).

13. Somewhat tangential to, yet resonant with, Barfield’s point, van den Berg describes one aspect of the process of human individuation over the past few centuries: “James Joyce used as much space to describe the internal adventures of less than a day than Rousseau used to relate the story of half a life. The inner self, which in Rousseau’s time was a simple, soberly filled, airy space, has become ever more crowded. Permanent residents have even been admitted; at first, only the parents, who could not stand being outside any longer, required shelter, finally it was the entire ancestry. As a result the space was divided, partitions were raised, and curtains appeared where in earlier days a free view was possible. The inner self grew into a complicated apartment building. The psychologists of our century, scouts of these inner rooms, could not finish describing all the things their astonished eyes saw. It did not take them long to surpass Joyce, and their work became endless in principle. The exploration of one apartment appeared to disturb another; and if the exploration moved to the next place, the first one required attention. Something fell down or a threat was uttered; there was always something. The inner life was like a haunted house. But what else could it be? It contained everything. Everything extraneous had been put into it. The entire history of mankind had to be the history of the individual. Everything that had previously belonged to everybody, everything that had been collective property and had existed in the world in which everyone lived, had to be contained by the individual. it could not be expected that things would be quiet in the inner self” (van den Berg 1961, p. 232).

14. The word “picturesque”, which is recorded as first appearing in 1703 and became widely used in the Romantic era, testifies to the ideal aesthetic distance Barfield refers to. On one hand, it suggests detachment, inasmuch as the world can now be *looked at* as an independent object by the observer, like a picture hanging on the wall. But, on the other hand, a picture or painting was itself appreciated as a production of the human spirit.

15. Figure 23.4 credit: Mary and Jon Hirschfeld Workshop (CC BY 2.0), via Wikimedia Commons.

16. Figure 23.5 credit: Metropolitan Museum of Art (CC0 1.0 Universal Public Domain Dedication).

17. Figure 23.6 credit: From the National Archaeological Museum of Greece in Athens (CC0 1.0 Universal Public Domain Dedication).

18. This nonlinear character of the evolution of consciousness may remind the reader of our discussion of “mosaic evolution” in Chapter 19 (“Development Writ Large”), where we heard this (drawing on the work of Craig Holdrege): When something dramatically new arises in the fossil record, it is typically foreshadowed by fragmentary “premonitions” in various taxonomic groups, some of which may then go extinct. There is no smooth, continuous, single line of development leading to the new form, which may arise not only rather suddenly, but also as a novel synthesis and transformation of the earlier, scattered, premonitory gestures.

Sources

Barfield, Owen (1963). *Worlds Apart: A Dialogue of the 1960's*. Middletown CT: Wesleyan University Press.

Barfield, Owen (1965). *Saving the Appearances.* New York: Harcourt, Brace and World. Originally published in 1957.

Barfield, Owen (1967). *History in English Words*. Foreword to revised, 1967 edition by W. H. Auden. Great Barrington MA: Lindisfarne. Originally published in 1926.

Barfield, Owen (1973). *Poetic Diction: A Study in Meaning.* Middletown CT: Wesleyan University Press. Originally published in 1928.

Barfield, Owen (1977). *The Rediscovery of Meaning, and Other Essays*. Middletown CT: Wesleyan University Press.

Barfield, Owen (1981). "The Nature of Meaning", *Seven* vol. 2, pp. 32-43.

Butterfield, Herbert (1957). *The Origins of Modern Science 1300-1800*, revised edition. New York: Free Press.

Emerson, Ralph Waldo (1836). *Nature*. Boston: James Munroe and Company. https://archive.org/details/naturemunroe00emerrich

Gombrich, E. H. (1989). *The Story of Art*, fifteenth edition. Oxford: Phaidon.

Shelley, Percy Bysshe (1840). "A Defence of Poetry", in *Essays, Letters from Abroad, Translations and Fragments*, by Percy Bysshe Shelley, edited by Mary Wollstonecraft Shelley. London: Edward Moxon. "A Defence of Poetry" was originally written in 1821 and published posthumously. Text is available at https://www.gutenberg.org/ebooks/5428

Snell, Bruno (1960). *The Discovery of the Mind*, translated by T. G. Rosenmeyer. New York: Harper and Row. Originally published in 1953.

Talbott, Stephen (1995). *The Future Does Not Compute: Transcending the Machines in Our Midst*. Sebastopol CA: O'Reilly and Associates. Available online at https://netfuture.org/fdnc/.

Talbott, Stephen L. (2018). "A Physicist, a Philologist, and the Meaning of Life: Do We Have a Home in the Vast Cosmos?". https://bwo.life/org/comm/ar/2018/meaning_33.htm

van den Berg, J. H. (1961). *The Changing Nature of Man: Introduction to a Historical Psychology*. New York: Dell Publishing.

Vernon, Mark (2019). *A Secret History of Christianity: Jesus, the Last Inkling, and the Evolution of Consciousness*. Arlesford, Hampshire, UK: John Hunt Publishing.

White, John (1972). *The Birth and Rebirth of Pictorial Space*. New York: Harper and Row.

CHAPTER 24

How the World Lends Itself to Our Knowing

All physical scientists, in an effort to understand reality, take their stand upon a tiny island of knowledge, surrounded by an immense, fathomless sea of ignorance. The island is forever threatened and re-shaped by revelatory eruptions from the surrounding deep.

According to the celebrated physicist, Richard Feynman, "we have no knowledge of what energy *is*" (Feynman et al. 1963). Nor, for that matter, do we know what a *force* is. And the same is true of all the foundational terms of physics. *Matter*, the supposedly solid ground of material reality, remains an enigma that has only grown more perplexing along with advances in quantum physics. Other basic terms such as “space”, “time”, and “field” — while perfectly workable as conceptual black boxes in the context of the physicist’s narrow mathematical aspirations — are not themselves so much elements of adequate explanation as they are perplexities in need of explanation.

The general fact of *chemical transformation*, by which, for example, hydrogen and oxygen gases can be made (in the right proportions and in the presence of a flame) to “explode” into water, remains for our present understanding something like a miracle. The supposedly explanatory “particles” involved — which we know only as theoretical constructs altogether lacking sensible qualities — are said to rearrange themselves in an instant. According to the standard picture, the rearrangement of the qualityless particles somehow yields a radical transformation in the qualities of the reacting gases, releasing in the process a great amount of Feynman’s unknown energy. And so, gaseous elements of the atmosphere, flown through by birds, transmute before our uncomprehending eyes into a fluid element of the sea, swum through by fishes.

The mysteries we confront are as great as the universe itself. Physical laws — and, in general, the rational coherence and order of the world — remain puzzles for us at least as profound as they were for Galileo and Newton. And so also with the ever-growing conundrum of human thought — that “unnatural quirk” in the universe through which, it just so happens, the universe invites understanding of itself. As for the “Big Bang”, it brings no more lucidity to the question of origins than “God made it so”.

It would be a stretch to think that any of our “settled” science is immune to serious reconsideration, depending on whatever revelations eventually illuminate these fundamental questions. I am not talking about a need to recalculate, say, the numerical value of the gravitational constant, but rather our understanding of the character of the physical cosmos and the manner of our participation in it as knowers. Or the significance, among scientists, of their paradoxical commitment to a materialist dogma in which no one can define “material” while all do consider themselves *thinkers* who take their own scientific descriptions to be both *meaningful* and true to the world’s reality.

In sum: our accumulating grasp of (mostly technological) know-how, stunning as it is in practical terms, is nevertheless a power enveloped by profound ignorance. What little understanding we have of the world we so skillfully manipulate is at every moment subject to modification by whatever yet-unimagined insights may eventually bring clarity to this or that enigmatic term at the root of our science.

And yet — isn't it odd? — we find it so natural and easy to forget all this! In our primary cognitive enterprises — science, education, religion — training for the young focuses on what we already know, or think we know, rather than on our ignorance and the corresponding promise of new understanding. On my own part, I feel an obligation at least to acknowledge the largely unaddressed mysteries shadowing our understanding.

Getting to know the world of experience

Stand anywhere in nature and observe the scene. It can be a mountain or meadow, sea or sky, lake or desert — or a city street. Then ask yourself: what would remain of the scene if you were to remove every quality from your surroundings?

To ask about qualities is not merely to inquire into our own subjectivity or aesthetic sensibilities. Rather, it has to do with the bedrock character of the world we perceive, bearing on everything from the luxuriant Amazon rain forest to the barren surface of the moon. Wherever we are, what would exist for us if there were no qualities? Does any material *thing* in the known cosmos present itself other than through qualities?

It is not a difficult question. Would that tree be there in what we consider a *material* sense if there were no color of the leaves, no felt hardness of the trunk, no color and texture of the bark, no whispering of the breeze among the leaves, no smell of sap, wood, or flower, no possibility of song from birds flitting among the branches? Do we see, hear, touch, smell, or otherwise sense anything in the world apart from its qualities? Could we speak of a thing's form, substance, or even its existence if it did not present a qualitative, sense-perceptible face to us?

The hardest part of all this talk about qualities for most people lies in their feeling that the solid external reality of things is being denied. But to point to the qualitative nature of the sensed world is not to question its reality, or its solidity, or its otherness. It is merely to acknowledge that real solidity — the only solidity we are given in experience and can collectively verify as an objective aspect of reality — is *felt solidity*. The sensed hardness of things is no less a perceptible quality than the taste, color, or sound of things.

What tends to be missed here is that the qualities of nature are not the private individual's subjective contribution, but rather belong to the world's objective reality that we collectively share. We do not need to invent an additional reality — minuscule bits of mindless and qualityless stuff (particles) somehow *behind* what we experience — in order to account for the trans-individual objectivity (otherness) of the world's expressive qualities. Nor has it has ever been clear how we could possibly account for qualities by starting with imperceptible entities that, by virtue of their imperceptibility, are utterly without qualities.

To say that the world we know is qualitative is not to doubt its substantial reality. It is only to say that this reality is irreducibly qualitative. We think that this claim contradicts the world's substantiality only when we *begin* with the assumption that qualities are merely subjective and insubstantial. But qualities are not features that exist only “in our heads”. If we believe the perceptible world is really and objectively there before us, then we must believe that qualities are really and objectively there before us also, since we would have no perceptible world without its qualities.

So we come back to the perfectly straightforward question: “Does anything exist materially, available to an empirical (experience-based) science, except as a presentation of qualities?” Would we have quantities to play with if there were no qualities from which to abstract them? And would we know what our mathematical formulae were about — what they meant — if we could not restore to our thinking the qualitative contexts from which they were abstracted? Numbers alone do not give us a material world.

I think the conclusion you will come to is inescapable: whatever knowledge of the world we manage to gain is rooted in qualitative appearances, and the world would lose its reality for us — it would no longer be there for scientific investigation — were its qualities to vanish.

Given the more or less determined yet never fulfilled resolve among scientists from Galileo onward to have a science without qualities, it would seem that the integrity of science as a respectable knowledge enterprise rather than an empty pretense hangs on our answer to the question, “Would anything be left to investigate if we could be true to our ideals and remove all qualities from our science?”

Because the answer is that nothing would be left, we never do in fact succeed in having a science without qualities. In Chapter 13 I pointed out how nonsensical, if not also humorous, are the ways in which otherwise serious thinkers end up falsely projecting qualities into their non-perceived, purely theoretical constructs — all so that they can seem to have something, rather than nothing, to talk about.[1]

We know the world through thinking as well as sensing

There are two primary portals for our experiential knowledge of the world: first our senses, and then the thinking that conceptually orders the diverse contents of the senses, bringing them to meaningful and coherent appearance. If we could not perceive qualities through our senses, as I suggested in the previous section, we would not have a world. But it is equally true that without a conceptual ordering of what we receive through the senses, we again would have no world.

If we are truly to recognize something — a *this* as opposed to a *that* of a particular sort — we must be able to form *some* conception of what we are beholding. Which is to say: we must grasp the ideas that inform and are inherent in what we are beholding. The phenomenon can present itself to us as a given reality only so far as its real and inherent thought-content becomes at the same time *our* thought-content. To see a soaring hawk while having no idea of organism, bird, wing, flight, raptor, predation, air, gravity, matter, and so on, would not be to *see a hawk*.

The appropriate concepts are our power of recognition and understanding, and without them we have no such power. This is true whether we are apprehending ideal (idea-like) laws governing material interactions, or the ideal coherence of a single leaf or grain of sand.

We would not recognize a tree if, in looking up toward a cluster of green leaves, we had no ideas to tell us that the relation of the leaves to branch, trunk, and roots is very different from their relation to the visually adjacent patch of sky-blue color. We could in general recognize nothing of the tree at all if we had no idea of the thought-relations constituting a tree as what it is.

To stare in absolute, thought-less incomprehension at the scene around us would be to stare at a meaningless blur — or not even that, since, in our thoughtlessness, we would lack the concept of a “blur”. Things come to meaningful appearance only by virtue of their distinct and interwoven meanings; we recognize them by means of the ideas lending them specific form and significance, through which we can identify them as being the kind of things they are. (“Oh, *that’s* what I’m seeing!”)

In only slightly different words: we could have no idea of things that, in their own nature, were entirely non-ideational. “A reality completely independent of the mind which conceives it, sees or feels it,” wrote the French mathematician and physicist Henri Poincaré, “is an impossibility” (Poincaré 1913, Introduction). And the traditionalist thinker, René Guénon, distilled the matter to its essence when he wrote: “If the idea, to the extent that it is true and adequate, shares in the nature of the thing, it is because, conversely, the thing itself also shares in the nature of the idea” (quoted in Burckhardt 1987, p. 14n).

The main point here — that ideas belong to the innermost nature of the world — seems extraordinarily difficult for us moderns to take hold of. Perhaps we await only an emphatic snap of the fingers to awaken us from our trance and enable us to see what is painfully obvious: if we, with our human thinking, can *make sense of the world*, it can only be because the world itself is in the business of *making sense*. Ask yourself: how could it be otherwise? And yet the fact that thoughts are not merely the private property of individuals, but also come to manifestation within the world around us, is virtually unapproachable for most of us today.[2]

I don’t suppose there could be a more startling disconnect than when knowledge seekers aim to *articulate a conceptual understanding of a world they consider inherently meaningless*. A conceptual articulation, after all, is nothing other than the working out of a pattern of interwoven meanings. A truly meaningless world would offer no purchase for this effort.

My repetition in these last paragraphs has been intentional, because the truth so easily escapes us. Let this be the sum of the matter:

> *Anything whose objective and true nature we can apprehend only through revealing description, including scientific description, can hardly be said to possess a nature independent of mind, thought, language, or meaning.*

Two other notes. First, we commonly assume that our perception gives us “things” directly and mindlessly, about which we then think and form theories. But a truth widely recognized by those who study cognition is that we do not even have “things” except through an activity of thinking — not necessarily a conscious thinking, but rather a thinking that, ever since childhood, has increasingly informed our senses. This thinking often shapes what we perceive without our being aware of the role of thought.

But, with proper attention, it is rather easy to catch this thoughtful, formative activity of perception “in the act” so as to become aware of it.[3]

Finally, whatever the processes of human cognition, we should not think that the world itself has distinct "parts", the sensible and the thoughtful. We can no more imagine something sensible without thought than we can imagine substance without form. We can, of course, distinguish between the two aspects. But as soon as we ask "what it is" that meets our senses quite apart from its thoughtful coherence, we have a problem. To say anything at all about what it is would be to characterize it with thought, so we would no longer be talking about a sensible content apart from thought.

I don't think there is any way around this, nor need there be. The world is a unity. It resists every rigid dualism. But surely we can say — as a matter of distinction rather than pulling apart — that whatever meets our senses must be inherently bound up with thinking, much as substance is inherently bound up with form.

Is the world a dualism of appearance and reality?

We have seen that the only world we could ever know is known interiorly, through sense perception and thinking. It is a "marriage of sense and thought" (Edelglass et al. 1997). Of course, our knowing of the world requires other interior capacities as well, such as those of imagination and will. But the main point at the moment is the rather obvious one that all our knowing calls upon interior capacities — powers of inner activity that presuppose consciousness.

By "consciousness" I include everything on the spectrum running from the unconscious to those contents of which we are most fully aware. What unites everything along this spectrum is its potential for being an interior content we are aware of. Which is to say rather paradoxically that the unconscious shares in the nature of consciousness. We do in fact find ourselves often raising to consciousness interior contents that *had been* unconscious (see Principle #8 in Chapter 25).

Since both our perceiving and thinking are functions of consciousness, the manifest world is a world consciously experienced. And since we all share the practical, day-to-day conviction that the world of our conscious experience is, in a direct and unmediated sense, the real world — not a mere picture or representation of the world, but a world with which we routinely, materially, and consequentially engage in the immediate terms of our experience — the most straightforward and consistent conclusion is that the world itself, *in its own nature*, is phenomenal. It is a world whose true being is its *appearing*, its lighting up within experience. Qualitative and thought-full, it comes to its own characteristic expression — achieves its own reality, or existence — only within what we might call the *interior dimension*.[4]

But this straightforward conclusion collides with a centuries-long mental habit that tells us we look out upon a world of mindless objects utterly independent of, and unlike, our cognizing selves — objects wholly alien to our own inner being. In fact, these objects are imagined to be so alien that our perception of them cannot be trusted. Who has not heard the "deceptive" subjectivity of human perception contrasted with the solid, trustworthy reality of mindless physical objects?

The common suggestion, then, is that we have two different worlds: the *subjective* world of appearances — appearances not only mediated by, but also unknowably transformed by, our nervous systems — and a world of *real things* somehow hidden behind the terms of our experience. This gives us a secondary dualism — one of appearance and reality — descended from the primary "Cartesian dualism" of mind and matter.[5] From this point of view, untrustworthy appearances are all we have, at least in any direct sense. Objective reality, on the other hand, is — well, it is presumably out there *somewhere*.

Our cognition places us in the world, not a mere representation of it

One rather sticky problem with the appearance/reality dualism is that this would seem to make reality unavailable to an experience-based (empirical) science. But a more immediate issue is that the supposed second reality hidden behind the appearances contradicts our natural, seemingly irrepressible, and well-supported conviction that we directly experience the real world.

Regarding this last point: nothing in our perception hints at the existence of a second world — a *real* world contrasting with appearances. A perceived tree appears *itself to be* the tree. So also the stream I sometimes sit alongside. If I pick up a small stone and toss it into the water, I perceive both the object and my own arm in picking up the stone and throwing it, and I likewise perceive the trajectory of the stone in relation to earthly gravity, the wind, and the energy at work in my muscles. I can be sure that, exactly as observed — and exactly where observed — the stone and all the other elements of the scene, from my arm to the water, are fully "respecting" the laws of nature. That is, these elements are lawful *in their own immediate, experiential terms* — without my needing to refer to some hidden, non-qualitative, non-experienceable reality behind the appearances.[6]

So the world I perceive shows no sign of actually being inside my head either literally, or as a reduced representation, or as an illusion, nor any sign of somehow referring to an unknown substratum lying behind the appearances. Rather, perceived objects testify with overwhelming force to their occurrence, *in their full-bodied presence and reality*, right where and as they are given in qualitative, thought-full experience. In other words, when you and I try to picture the "interior" space of our consciousness, we must image a space substantially (but not wholly) shared with others; and within this shared space of consciousness we find the reality of the material world.

We can put this in either of two complementary ways. We can say, in the first place, that our experience of the world occurs not merely "in here", in some purely private space, but rather occurs in the world itself. Or we can say: the world itself naturally occurs within the *interior dimension* of experience in which we all (along with other creatures) participate.

The private aspects of the experience stem in part from the fact that it comes to us via our personal sense organs, located in space and giving us, for example, a particular angle of view upon a tree. Subjective aspects may also stem from, among other things, defects in our sense organs, such as the severe tinnitus I experience. But we do not find these subjective aspects of our experience bringing into question the objective character of the world we share with others. The English philologist and philosopher, Owen Barfield, has put it this way:

> I am hit violently on the head and, in the same moment, perceive a bright light to be there. Later on I reflect that the light was "not really there." Even if I had lived all my life on a desert island where there was no-one to compare notes with, I might do as much. No doubt I should learn by experience to distinguish the first kind of light from the more practicable light of day or the thunderbolt, and should soon give up hitting myself on the head at sunset when I needed light to go on working by (Barfield 1965, pp. 19-20).

We have no ability even to conceive how an objective thing might exist outside the possibilities of experience. To conceive its supposedly alien character in order to announce our belief in it would be to realize it in the only place it could be realized — within consciousness. So it wouldn't be alien after all.

I have already mentioned that, in the daily routine of our lives, we are all convinced that our experience as knowers presents us with the actual contents of the real world. We are given *within consciousness* things we know at the same time to be objectively *out there*. But we do not succeed very well, intellectually, in holding on to this double aspect of our experience. The effort to do so, therefore, can be an excellent exercise. We can try to grasp simultaneously both of the following truths, each of which by itself seems a self-evident aspect of our experience, whereas the two conjoined do violence to our most entrenched habits of thought. Looking out upon a natural scene (preferably one with movement, as of clouds or a stream or wind-blown trees), we can think:

- *This presentation of nature, with its objective and collectively verifiable aspects, is itself the real material world in which I and others live, write poetry, and do scientific experiments.*

But also:

- *This presentation of nature is occurring within my consciousness*.

The ultimate demonstration of the compatibility of these two truths is up to those individuals who actually make them a matter of experience. The exercise is best done briefly and repeatedly, but with thoughtful concentration, over a long period. But be assured: at the point where you have deeply taken in both truths and have been able to hold them together in harmony, you will have overcome much of the pathology in modern human experience.

All this is extraordinarily important. But it is also extraordinarily difficult for contemporary minds to accept. Nevertheless, allow me to state the matter once more: the "view" of the world we are given through our thought-informed senses is not just a view, or representation, of the world. It actually *is* the world — the world in which we are present and from which our own bodies are made. Or perhaps it would be even better to say (with a view toward the following section): it is our direct participation in the creative activity giving rise to a world possessing the character of "experiential substance" — a world that is from the beginning an expression of interior activity and that can be creatively participated in by means of our own interior, expressive activity.

We cognize the world by participating in its creation

There can be no overstating how dramatic and unexpected is the view set forth above. It is one thing to imagine that our eyes are little camera-like devices producing an image that someone, somewhere, somehow, manages to view and interpret as a representation of a mind-independent world. But it is quite another to recognize that, through our eyes and other senses together with our thinking, the world itself takes up its existence in the *only place it can — within living experience*.

During the first third of the nineteenth century Samuel Taylor Coleridge had to have come to terms with the difference between reality and a representation of it when he suggested that our power of perceiving and knowing the natural world is a repetition in our own minds of the very same creative activity through which the world came to exist and is sustained.[7]

In other words, so far as we truly and imaginatively perceive the world, we do not merely encounter it from outside. With our cognitional faculties, we stand within it, as in some sense our own creation. After all — as I have been suggesting above — it is not that we “snap a picture” of an independently existing world. We have the very world itself through our cognitional activity. This suggests that, through the creative aspect of our perception, we may “do our own bit” in shaping the world’s coming to reality, just as each of us plays his own role in making human society what it is. For more on this, see Chapter 24, “The Evolution of Consciousness”.

How much we have had to pay for the anemic belief that our senses give us mere picture-like representations of an alien world! But everything changes when we realize that, just as a boulder on a mountainside is fully and seamlessly embedded in the surrounding world of wind, water, light, and gravity, so, too, our own cognition and expressive powers embed us as knowing participants within a reality of universal expressiveness, and do not confront us with a mere representation of it.

We can notice in general that everything we make into a content of our own experience requires a re-enacting of something like the interior activity that first produced that content. This re-enacting is, for example, the way one human being experiences the content of another’s mind. If we attend a lecture (and are paying attention), we follow along by bringing the speaker’s thought-content alive as the content of our own minds. So far as we do this faithfully, we live within the same thought-world as the speaker, not a copy of it.[8]

But something like this must also be true of the qualities and thought that constitute the interior dimension of the world as a whole. Here, too, our possibility of seeing and understanding depends on our ability to re-enliven the one world’s interior by participating directly in it through the activity of our own interior — in particular, our sensing and thinking.

Coleridge's remark can help us keep in mind just how radical all this is. If we, in bringing the contents of the world alive within our own experience, must participate in the creative activity through which these contents are originated and sustained, and if this does not mean creating some kind of private copy, but rather being active in the one world's original and ever-evolving manifestation of itself — well, then, this places us in a position of high responsibility indeed.

The world as a form of speech

Human language gives us our most immediately accessible picture of the marriage of sense and thought. The outer, sense-perceptible sounds of speech are shone through by an inner meaning. Only when we receive the words as informed by their meaning do we have the sensible phenomenon of language at all. And the point of all I have said earlier is that this marriage of sense and thought, so easily recognizable in speech, reflects the general character of the world into which we were born.

We might say, then, that the world has the character of language. It is meaningful expression. Or, in more ancient terminology, it has the character of the Logos. The whole universe, in its essential nature, is a continual coming into being, which is also to say, a continual expression or unfolding of meaning, and we are children of this meaning. In this sense, our being born is our being *spoken* into earthly existence.

Numerous creation stories from around the globe have pictured the genesis of the world and all its creatures as occurring through the spoken word (or song). As we saw in the chapter on "The Evolution of Consciousness", this is how the ancients experienced the world — as thought-full expression — and the experience was lost only in relatively recent history.

Language, then, is not a mere tool we somehow invented. Our minds and our speech precipitated out of language — a language of nature in itself too profound for words. We were spoken into being so that we might eventually learn to speak for ourselves, however crudely. All along the way, the meanings inherent in the world nurtured us toward this end. It would be a useful exercise to trace how, in so many naive discussions of the supposed origin of language — that is, in discussions about how language is thought somehow to have arisen in creatures initially lacking any form of it — we find a hidden assumption that language already existed before its supposed origin.

For example, a grunt or a finger-pointing or an "excited" state of jumping up and down is often assumed (quite rightly) to have some initial, unaccounted-for *meaning*, rather than being merely part of a chain of physical causes and effects. So these actions are, from the very beginning, taken to be significant *gestures*, and therefore are already being imagined as language.

This is fine as long as we realize what we are doing. The grunt and finger-pointing are not the means whereby the non-meaningful becomes meaningful, or non-language becomes language, but rather stages upon the path by which language comes to ever greater clarity and focus in human consciousness.

This is why Owen Barfield, the student of the evolution of consciousness, once remarked that to ask about the origin of language "is like asking for the origin of origin". We had first to be spoken in the deepest and most meaningful language before we could internalize that creative speech and make it our own.

A similar understanding shines through remarks by the German philosopher and linguist, Wilhelm von Humboldt, a contemporary of Coleridge:

> It is my overwhelming conviction that language must be viewed as having been placed in man: For as a product of his reason in the clarity of consciousness it is not explicable. It does not help to grant thousands upon thousands of years for the purpose of its invention … For man to truly understand even a single word, not as a mere physical outburst, but as sound articulating a concept, language must already exist as a whole within him. There is nothing isolated in language, each of its elements only appears as part of a whole. As natural as it may seem to assume that languages develop, if they were also thus to be invented, this could only happen all at once. Man is only man through language; in order to invent language he would have to have already been man.[9]

This interwoven unity and indivisibility of language ultimately extends to all languages, human or otherwise, and even to the entire cosmos as "the book of nature". Language, we might say, is One, and so also is Logos, and so also is the world that allows itself to be brought to light only through language. It is from this all-encompassing matrix of meaning that we, like all other organisms, emerged as meaning-bearers into a world of meaning. But it is not hard to realize that, as conscious cognizers — as speakers now increasingly capable of giving proper (or improper) names to things — it is we especially who hold the future within the creative fires of our hearts. And there, surely, is where the deepest words are even now being spoken.

Where are we now?

Epistemology Is Not Easy

We have, throughout this book, been bumping up against questions of epistemology: How are we situated in the world as knowers? How does our knowing emerge from our experience, and what is the relation between the resulting knowledge and the world's reality? The questions began already in the Preface, where I suggested that a good part of our thinking about the molecular realm is really just an illegitimate projection of our qualitative experience of the world onto the blank screen of an unknown world of particles. This particle-world is falsely imagined to be non-qualitative and mind-independent and to exist somehow "behind" our experience. I explicitly reinforced this concern in Chapter 13 by offering examples of the projection, and throughout the book I have appealed to an interior (meaningful, ideal, agential, and purposive) dimension of living activity that is hard to square with current notions about what constitutes acceptable biological explanation.

There is not much in their training to encourage biologists to entertain questions on this fundamental level. And there is a great deal in the powerful taboo against non-materialist thought that discourages such questions. Nevertheless, I have tried to show in this chapter that even a cursory look at the role of qualities and thought in our engagement with the world (including our scientific engagement with the world) decisively undermines the entire materialist framework of current biology. This book, you might say, has been an exercise in raising questions that are simply invisible — because forbidden — under the present scientific regime.

I realize that some of the questions I raise may seem almost surreal to those raised and disciplined within the current environment. (For example, "With whom are we in conversation as we engage with the world around us?".) But a science that is altogether closed off from unfamiliar questions — especially when there is a strong case to be made for asking those questions — is not a healthy science. And surely we should never make it a requirement to have a full answer to a question before asking it.

In the next, concluding chapter I will try to articulate a number of principles of biological understanding that can be recognized once we decide to ignore the above-mentioned taboo and go wherever organisms lead us. These are principles, I trust, that will immediately be recognized as naturally arising from one or another part of the book now behind us.

Notes

1. "But science works — nearly miraculously!" This is emphatically true. It works because working is just about the sole intent of the methods of those sciences whose working impresses us so much. But technological savvy — making things that work — is a very different matter from a fundamental understanding of the character of the world we live in. Finding ways to manipulate the world successfully is not at all the same as understanding what sort of things we are manipulating and how we might relate to them beyond our capacity for manipulation. In many situations mere trial and error is sufficient for successful manipulation. So, too, are scientific models that are known to falsify reality in one way or another.

John Dalton's theory of the indivisible, indestructible atom and Niels Bohr's theory of the "solar-system" atom both served to further the manipulative powers of science, and both found crucial application in the experimental domains from which they were derived. But neither of them would possess any respectability if seriously put forward today.

2. The philologist and historian of consciousness, Owen Barfield, in the second lecture of his little book, *Speaker's Meaning*, pointed out that, up until the Scientific Revolution, the conviction that ideas were the private property of individuals would have been fully as unapproachable as is the conviction, for us, that ideas belong to the objective world. The "common sense" of every age can be remarkably difficult to come to terms with, or even to recognize as such. So we tend to be trapped within our own cultural era. The best escape from the trap is to become literate about how earlier eras differed from our own. And that literacy is not achieved merely by spinning childish tales about our own triumphs over the universal ignorance of our forebears. See Chapter 23, ("The Evolution of Consciousness").

3. See in particular the section, "How do things around us become what they are?" in Chapter 13 ("All Science Must Be Rooted in Experience"). If anyone should remain skeptical of this, I would strongly suggest reading Chapter 4 ("Intentionality") by philosopher Ronald Brady in the online, freely accessible book, *Being on Earth: Practice In Tending the Appearances* (Maier et al. 2006).

4. It is certainly true that a person who is blind or deaf or who has had traumatic encounters in nature might have experiences of the world differing from those of someone whose senses are functioning "normally". There is in general a huge range of potentials among persons of all sorts. Mozart would have ("normally") experienced the world of sound and music to a depth I cannot imagine, just as Picasso would have experienced the world of visual form in ways incomprehensible to me. I do not have a bat's sonar-like sense, nor an insect's infrared sense. The world lends its potentials of experience to all creatures according to their capacity. But we all find ourselves living side-by-side in *one world* — a consistent and shared world with diverse yet harmonious potentials of experience.

This interior, experiential character of the world would make no sense — would find no realization — in a universe that was not fundamentally a universe of beings rather than things. And, as we saw in Chapter 23 ("The Evolution of Consciousness"), throughout most of our long history, going back at least as far as the age of myth, a world of beings is exactly what humans directly experienced — long before our ancestors had a capacity for theorizing or inventing fanciful causal explanations. Not many are interested in at least inquiring whether there might be something pathological in our own strong inclination to imagine a world of things rather than beings.

5. During the first half of the 1600s, the French philosopher René Descartes distinguished between “extended stuff” and “thinking stuff” — and did so as if they were separable and disconnected substances having little or nothing in common. This is said to be the source of the “dualism” that so many today, for good reason, would like to disown. Having echoed down through the last several centuries, dualistic thinking has crystallized especially in what we think of as the mind/body problem and, more generally, the mental/physical dichotomy.

Nearly all scientists today disavow “Cartesian dualism”, yet nearly all live intellectually by means of it. There is a very real sense in which Descartes’ cleaving stroke through the heart of reality has been almost universally accepted — perhaps most of all among materialist-minded biologists. That is, they seem to have felt they must accept the stroke as a kind of *fait accompli* and then try to live with the violence thereby done to the unity and harmony of the world. They merely choose: which half of this improbably fractured whole shall they accept and which half reject? And so the “material” they embrace is dualistic material, bequeathed to them by the Cartesian sundering of mind from matter. Likewise, the mind they reject is dualistic mind.

Materialists they may be, but their materialism is defined by the dualism that has been drilled into our habits of thought and perception. Instead of going back and searching for a different, non-dualistic way forward, they have accepted the original, dualistic fractionation of a living, unified reality, and been content merely to carry a torch for just one of its mutually estranged aspects.

A way forward has already been indicated in the foregoing. Instead of a dualism of mind and matter, we could acknowledge the actual process of our knowing, with its intimate marriage of thought and sense. Our own experience presents us with nothing incompatible or problematic about this marriage. The only problem is that we have been trained by our dualistic habits to think of substance as inert, mindlessly solid “stuff” whose inherent, well-formed powers of lawful (ideal) interaction can be conveniently ignored whenever we are considering the nature of material reality.

But, contrary to this prejudice, we find it impossible even to conceive a substance, or interaction of substances, that is not already an expression of meaningful form. This is the point made in the previous sections — that we perceive nothing without the aid of form-giving thought. We should ask ourselves: “Where do we ever encounter substance that is not a manifestation of specific, intelligible form?”

The obstacle for our understanding of all this lies in the unconsidered *presupposition* that the problem of knowing is the problem of how our “minds in here” can apprehend “mindless substance out there”. But this is a dualistic assumption made *before* one looks at the actual process of knowing. The dualistic stance is imposed on the analysis in advance, defining the entire shape of the philosophical problem.

The philosopher Ronald Brady, in a posthumous treatise titled “How We Make Sense of the World” (Brady 2016), succinctly summarized the issue this way:

◆ “If the question is: ‘how can we know the world?’ or ‘how does the act of cognition take place?’ we cannot begin with the very ‘knowledge’ that this investigation should justify, or we investigate no more than the logical implications of our presuppositions. Epistemology … cannot begin from any positive knowledge of the world, but must suspend all such ‘knowing’ in order to examine the act of knowing itself … if we do begin from such ‘knowledge’ our epistemology will necessarily validate present sciences, and deny the possibility of any other form of science.”

◆ “Most modern approaches, for example, take their starting-point from the apparent distinction between the thinking subject and the world external to that subject, and thus formulate epistemology after a Cartesian or Neo-Kantian framework. In this formulation … the basic question of epistemology becomes: ‘what is the relation of thinking to being?’ or ‘what is the relation of subjective consciousness to external or objective reality?’ These questions arise from the assumed separation of the two — that is, thinking attempts to know the world of objective reality, which world is itself totally independent of thinking. In such a formulation, however, we [assume that we] already know something of that world (such as its difference from thinking), and the problem is created by what we know — that is, the distance between the thinking and its object.”

◆ “Since we cannot take the results of previous cognition for granted when we attempt to grasp cognition itself, another formulation of the problem is necessary. If we simply propose that knowledge is immanent in human consciousness (if it is not, then we are not speaking about anything), the basic question of epistemology could be simply: How? What is the act of knowing? Thus we face toward our own act of cognition, and the investigation turns on the *self-observation of thinking*.”

6. We are free to theorize in terms of non-experienceable constructs. But we typically do so by at least implicitly making models out of them, *as if* they were experienceable things (such as the “particles” of particle physics). And such models — because they are based on non-experienced constructs abstracted from appearances and falsely conceived as if they were themselves actual appearances (phenomena) — always turn out in one way or another to be false to reality. (See Chapter 13.) They also vex us to no end, as in quantum physics.

There is no reason we should not investigate the appearances in all directions available to us, without limit. We can, for example, use instruments to explore the structure of forces at a level beneath the possibility of actual sight or touch. But the physics of the past century has taught us very well that we run into crippling trouble when we try to clothe unsensed theoretical constructs with sensible qualities, as we typically do when we talk about “particles” and then all too naturally assume that these must be capable of traveling from point A to point B through space (or through narrow slits) as if they were sense-perceptible things.

If the world is by nature an *appearing* world, then we betray reality when we talk about non-appearing things as if they were actual phenomena.

7. Coleridge wrote: “The primary Imagination I hold to be the living Power and prime Agent of all human Perception, and as a repetition in the finite mind of the eternal act of creation in the infinite I AM” (Coleridge 1906, Chapter 13). Coleridge was speaking from a deep Christian faith. I do not know any grounds for disparaging his way of stating the matter, but for the sake both of

simplicity and of remaining as far as possible within the terms of our contemporary powers of scientific observation and analysis, I have paraphrased his remark in the main text. Coleridge also wrote that

> the productive power, which is in nature as nature, is essentially one (i.e. of one kind) with the intelligence, which is in the human mind above nature (Coleridge 1969, pp. 497-98).

Coleridge (quite rightly!) considered this statement rather obscure. Fortunately, we can expand the remark in line with his own written annotation of it: the productive power of becoming which we discover in (or above) the finished products of nature is a power we can call "Nature", or "Agency". And this Agency above nature is akin to the intelligent Agency of the human being, which also stands above nature.

8. Regarding our attention to a lecture: it is also well known that we tend to mimic the lecturer's physical speech subliminally within our own vocal apparatus. As for copies of thoughts, it is well to realize that the conceptual elements are not material structures, and we cannot create multiple copies of them. What would be the "thing" we are copying? If we are paying attention to our own thinking and not theoretical brain states or whatever, we can hardly help realizing that, no matter how many times we return to the same concept, we are not multiplying copies of it, and the same is true when different people take up the same concept. We may accompany a concept with varying mental imagery, but the images are no more the concept than our pictures of a straight line are the concept of a straight line. All instances of the concept, as pure concept, are the *same* instance; they are numerically one, not many. Through our thinking we share, as it were, in "one spirit". It is a useful exercise to think of a pure concept (say, that of a straight line) while asking yourself, "How might this concept, *as a concept*, not as a mental picture, be multiplied?" It is difficult to imagine even what this might mean — or, at least, it is, so long as one stands within the actual experience of thinking, and not in some materialized image of it.

9. (Humboldt 1963, pp. 2-3). The translation from German is by Norman Skillen: https://journals.ucc.ie/index.php/scenario/article/view/scenario-16-1-10

Sources

Barfield, Owen (1965). *Saving the Appearances.* New York: Harcourt, Brace and World. Originally published in 1957.

Barfield, Owen (1967). *Speaker's Meaning.* Middletown CT: Wesleyan University Press.

Brady, Ronald H. (2016; posthumous). "How We Make Sense of the World: A Study in Rudolf Steiner's Epistemological Work". https://natureinstitute.org/ronald-h-brady/how-we-make-sense-of-the-world

Burckhardt, Titus (1987). *Mirror of the Intellect: Essays on Traditional Science & Sacred Art*, translated and edited by William Stoddart. Albany NY: State University of New York Press.

Coleridge, Samuel Taylor (1906). *Biographia Literaria*. London: J. M. Dent & Sons. Originally published in 1817.

Coleridge, Samuel Taylor (1969). *The Friend* vol. 1, edited by Barbara E. Rooke. Princeton: Princeton University Press (Bollingen Series LXXV); London: Routledge and Kegan Paul. Originally published in multi-volume editions of 1812 and 1818.

Edelglass, Stephen, Georg Maier, Hans Gebert and John Davy (1997). *The Marriage of Sense and Thought: Imaginative Participation in Science*. Hudson NY: Lindisfarne.

Feynman, Richard, Robert B. Leighton and Matthew Sands (1963). *The Feynman Lectures on Physics*, three volumes. Reading MA: Addison-Wesley.

Humboldt, Wilhelm von (1963). “Über das vergleichende Sprachstudium in Beziehung auf die verschiedenen Epochen der Sprachentwicklung”, in A. Flitzer and K. Giel, editors, *Werke in fünf Bänden*, Band 3, *Schriften zur Sprachphilosophie*, pp. 1-25. Darmstadt: Wissenschaftliche Buchgesellschaft.

Maier, Georg, Ronald Brady and Stephen Edelglass (2006). *Being on Earth: Practice In Tending the Appearances*. Freely available online version: https://natureinstitute.org/book/being-on-earth Hardcopy book is available from Logos Verlag Berlin (2008): http://www.logos-verlag.de/cgi-bin/engbuchmid?isbn=1887&lng=eng&id=

Poincaré, Henri (1913). *The Value of Science*, translated by George Bruce Halsted. https://ebooks.adelaide.edu.au/p/poincare/henri/value-of-science/

Chapter 25

Some Principles of Biological Understanding

Failure to recognize the reality of the world's interior dimension (Chapter 24, "How the World Lends Itself to Our Knowing") is the central fact underlying virtually all the limitations, illusions, and distortions of today's science. The twelve principles set forth in this chapter represent my effort to suggest some of the biological consequences of our acknowledging the interior dimension of the world.

Everything that distinguishes biology from the physical sciences derives in one way or another from the inner life of organisms. This remains true, I think, despite our difficulty in even beginning to imagine or characterize that inner life, and despite the fact that it must vary almost beyond all possibility of recognition between a one-celled organism and a human being.

Still, even those complex features commonly treated as definitive of life, such as the capacities for reproduction and self-maintenance (which I do not deal with here) are obvious manifestations of a well-directed wisdom, all the way down to the molecular level. This word "wisdom", when applied, say, to an amoeba, needs to be understood, not as an occasional and foolish eruption of empty sentiment, but rather as a pointer to effective, end-directed, and meaningful life processes that surely must be distinguished from, yet just as surely must be *evolutionarily continuous with,* conscious human intention and reason. What I mean by this will, I hope, become at least a little clearer in the discussion of the various principles given below.

Here are the principles we will look at:

- Principle #1: The world manifests itself, by nature, as a content of experience.
- Principle #2: Organisms are focal centers of agency.
- Principle #3: Biology, as a science of organized wholes, cannot be understood in terms of mechanized parts.
- Principle #4: Every organism is, first of all, a becoming, not a material structure.
- Principle #5: Biology requires portraits of specific character, not formulations based on universal law.
- Principle #6: Understanding the human self requires us to distinguish our own inner activity from its products.
- Principle #7: Organisms in general lack human-like selfhood.
- Principle #8: There exists a wide spectrum of consciousness in organisms.
- Principle #9: An organism has its own sort of interior dimension.
- Principle #10: A healthy science acknowledges the mystery implied by its own ignorance.
- Principle #11: The mystery of time is central to the life of organisms.
- Principle #12: Humans are a key to evolution.

We have, in the preceding chapter, already articulated our first principle of biological understanding — one that applies to the entire world within which organisms appear. I summarize it here:

Principle #1: EMPIRICISM

> ***THE WORLD MANIFESTS ITS TRUE BEING — GIVES EXPRESSION TO ITS REALITY — IN THE TERMS OF EXPERIENCE.*** *We perceive things through the appearance of their qualities upon the "stage" of our consciousness. The thinking with which we order our perceptions and render them coherent likewise occurs upon the stage of consciousness. And so our modern human understanding of the world consists of experiential contents, available to the knower within a self-aware consciousness. In the routine practice of our lives, we are all convinced that these experiential contents — however much they reflect our separate vantage points — are mutually consistent and constitute the reality of the world. The simplest assumption is that, whatever else we may say about it, the world itself, in its essential nature, has the character of sentient, cognitive experience. It occurs within an interior dimension. To deny this would be to render ourselves speechless about the world we live in. We were given our birth and our cognitive capacities by this world, and our experiential participation in its reality is our birthright.*

I tried to show in Chapter 13 how naturally we are led to suppose that the world available to science possesses the character of experiential content. This content may vary, depending on one's experiential capacity. It is not that different organisms exist in different worlds, but rather that the world's potential for manifestation is realized according to the character and capacity of each kind of being, just as two different humans — one of whom may be blind or deaf or lacking an education — can experience the same world differently, yet still find their worlds mutually consistent. We call "objective" that which can be reliably experienced and *collectively* verified by those with the requisite capacities. Pink elephants don't count.

Perhaps the truth has simply been too close to us for proper recognition. After all, to seek understanding is already to acknowledge something interior, accessible as a content of consciousness — something meaningful that can take the form of human comprehension while *at the same time* being a recognition of the truth of natural phenomena.

Then, too, virtually all scientists have long honored, at least in word, the ideal according to which science must be *empirical* — experience-based and grounded in observation and experiment. Such an ideal could have arisen only from a deep-seated confidence that our *experience* of the world is indeed an experience of the *world*. The founders of modern science presumably found the principle too self-evident to require much explicit defense.

And, again, it's obvious enough that the mathematically expressed regularities of physics are not only ideas (conceived in analogy to human *laws* by Francis Bacon during the Scientific Revolution) — but ideas we discover *in nature*. These regularities were the kind of thing that led the twentieth-century physicist, Sir James Jeans, to remark that "the Universe begins to look more like a great thought than like a great machine".

Strangely, though, however obvious the fact of the objective world's collectively verifiable experiential character may seem from some vantage points, any talk of the "experiential" and "interior" side of material phenomena strikes many as impossibly wrong-headed. And there is no denying the power of such talk to disrupt conventional thinking. Just consider its significance for biology. Suddenly endless discussions about the relation between organisms and the inanimate realm — between biology and physics — and, more particularly, discussions about the origin of our own cognitive faculties (how does one get mind from that which is utterly incommensurable with mind?), begin to look hopelessly askew in their materialist starting points.

Similarly, as discussed above: the fact of the world's nature as a content of experience undercuts the insistent and nearly universal habit of contrasting appearance with reality. What are we to make of this contrast if in fact it lies in the world's nature to be a world of *appearances to experience* — if the very substance and reality of the world is the substance and reality of appearances?

Principle #2: Agency

Organisms are focal centers of agency. *An organism is a more or less focused center of its own causal agency within a larger world of lawful regularity. This agency is an active, wise, and purposive power of activity reflecting the organism's needs, interests, and distinctive way of being. We could also speak of the organism as a focused center of self-realization — a telos-realizing being. An organism is a center of its own experience, inseparable from the larger world yet distinguishable from it, with its own way of experiencing and responding to the inner meaning of its world-surroundings. Not one of the key terms here — "agency", "purposive", "needs", "interests", "way of being", "self-realization" "experience" — is opaque to routine understanding, but neither is any of them wholly reducible to the conventional terms of physical explanation.*

The physicist is always looking for laws that are universal — the same everywhere. Viewing the world solely through the lens of such lawfulness, we certainly cannot expect to find local centers of agency possessing a unique lawfulness. Geological strata, rivers, and solar systems are not actively engaged in sustaining their own existence and do not have anything we would call their own local "need" or "interest" in the sense of an organism. No inanimate object flexibly *coordinates* physical causes in order to realize its own ends in the face of obstacles and unavoidable detours.

Much of this book consists of descriptions of organisms as agents and centers of their own activity, and these descriptions are presumably enough to give substance to the principle discussed here. We have also seen that many local contexts, including the cells of our bodies, can also be considered as *relatively* independent agents and centers of activity, while yet subordinate to the organism as a whole. Similarly, populations of organisms, including evolving organisms, may be seen as possessing their own, more broadly focused agency.

It is easy to see the difference between the universal and lawful regularity (mathematical or otherwise) of the inorganic world, on one hand, and the various foci of organic agency, on the other. And so it must be. Without a background of lawful regularity, the agency of organisms, including our own human agency, could not exist in any meaningful sense. If the results of our willed activity in the world were chaotic or unpredictable, then we could never coherently aim at achieving anything in particular. Our actions would make no sense.

Many have argued that the regularities of the universe rule out human freedom or any meaningful agency in organisms generally. But this is based on elaborate and tendential theoretical surmises about the world and its character, and about our relation to the world. Wouldn't it be much better to stick with the obvious and immediately experienced fact of effective agency, and then recognize that the world's regularities admirably serve this agency?[1]

The compatibility of lawful regularity and meaningful agency is displayed right before our eyes in the fact of speech. Speech, as a material phenomenon, arises from perfectly lawful bodily functioning, yet the intended meanings of the speech that employs the physical vocal apparatus cannot possibly be explained in terms of this apparatus.

The principle of agency is at the same time a principle of holism. The primary "unit" of agency is the organism as a whole. No activity of a part of an organism can be given a full or adequate explanation except through reference to this unit — reference, that is, to the purposive, meaningful activity of the whole. One aspect of this activity lies in the fact that parts are very often coordinated in the interest of the persistence of the whole.

This necessity to explain the part by reference to an encompassing unit of agency is absent in the physical sciences. The latter fully accept that the whole and its parts are intimately related, but the prevailing aim (or at least the aim that biologists are primarily aware of) is to reduce the whole to parts that can then be employed to explain the whole. In the kinetic theory of gases, for example, the pressure of the gas inside a bottle is said to be explained by the "impacts" of molecules against molecules. Our understanding of the gas pressure is supposed to derive from our understanding of the molecules and impacts. But we would never try to explain the molecules and impacts by citing the inherent drive of the gas to maintain itself (persist) at a particular pressure. Nor would we try to explain changes in the impacts by citing the gas' need to achieve a different state.

And this already carries us to our third principle.

Principle #3: Organicism (Non-mechanism)

> **BIOLOGY, AS A SCIENCE OF ORGANIZED WHOLES, CANNOT BE UNDERSTOOD IN TERMS OF MECHANIZED PARTS.** *“Mechanism treats every whole as resulting, by aggregation, from its parts; organicism treats the parts as resulting, by progressive development and individuation, from an antecedent whole” (Barfield 1977, p. 183). The agency of organisms, and their inner character generally, is intrinsic. We might think of this agency as a local outcropping, or increasingly individuated intensification, of the world’s interior dimension. A machine, as a machine, has no intrinsic meaning or agency. Such agency as it manifests lies in the idea and intention of its designer, imposed from outside through an arrangement of parts — parts lacking any inherent or natural ability to grow meaningfully together in that way. As soon as human maintenance and repair of any machine ceases, the machine progressively deteriorates toward dysfunction.[2] By contrast, when an organism suffers injury, it strives from within, as best it can, toward healing.*

Numerous biologists, philosophers, and others have enunciated this “organicist” principle, or something like it, over the past few hundred years. Not many biologists can have escaped hearing something like it on one occasion or another — and almost none will have heard the principle flatly disputed, simply because the effort of disputing it appears scarcely credible. And yet the main biological enterprise seems to roll on and on as if such an idea had never been given voice.[3]

The central problem here is not obscure or difficult to comprehend. Everything we know about living processes is missing in the machine. The parts of a machine show none of the character of an organ, cell, or organelle. They do not come into being organically from the progressive differentiation of an original whole, and do not result from the immanent formative power inherent in that whole. They are assembled by (human) activity external to the machine itself.

For many people, the computer seems to have played a major role in making the mechanical model of the organism more persuasive. Computers make the machine appear more “flexible” and “life-like”. But what we are really looking at in a computer is the remarkably detailed and intricate power of the human mind to structure its own thinking in a machine-like and logically precise way, so as to yield a program.

An inherent requirement of such a programmatic thought structure is matching hardware of the most rigid, precisely fabricated, unlifelike sort ever contrived by humankind. There is a reason why chip manufacturers must achieve extreme levels of cleanliness and air purity. The slightest contamination by an invisible particle of dust or smoke can render a chip — and the massive computer it may be part of — disastrously non-functional.

In a cell, molecules move with a high degree of freedom through a fluid medium. At that scale a computer designer, by contrast, needs to “freeze” movement, eliminating flexibility and free flow to the greatest degree possible. A cell or organism lives by means of the freedom of movement at the smaller scales, which is presumably part of what allows it to yield itself as a plastic instrument for the agency of the larger context — an agency reflecting the organism's current needs, interests, and way of being.

For more on the fluid, rhythmic, pulsing dynamism of living processes, see for example Chapter 5, "Our Bodies Are Formed Streams". That chapter, along with the foregoing discussion, suggests that, in organisms, more or less fixed structures take second place to processes of *becoming* — which brings us to our next principle.

Principle #4: Becoming

EVERY ORGANISM IS, FIRST OF ALL, A BECOMING, NOT A MATERIAL STRUCTURE. *Its life is a continual activity through which form becomes embodied in material substance and behavioral pattern. The physical structures of the mature falcon are not already there, materially, in the fertilized egg cell, but come into being through an activity of development and differentiation. This power to form a body — a power to materialize the form of an organism — is not itself a material thing. Its intelligible and functional (purposive) working testifies to the interior dimension of the organism. Material substance, once originated, may both constrain and enable further activity, but is not the source of that activity.*

I have mentioned several times elsewhere in this book how researchers can rearrange clumps of cells in many kinds of young embryo, and even insert the clumps in new places within the embryo, and then, through the ongoing developmental activity, those clumps adapt to their new places and new roles. The *process* of development clearly takes precedence over existing substance in the *origination* of the material structures of the organism. Once an organ (or limb or whatever) reaches sufficient maturity, it becomes a constraint on further development, which is a very different matter from the origination of organic structures.

Or consider the heart. Embryological development shows that

> the body does not behave like a plumber, first connecting the water pipes in a house and then turning the water on … the first blood-like liquid … simply trickles through gaps in the tissues … Preferred channels develop only very gradually as blood cells are deposited along the edges and eventually merge into the beginnings of vessel walls (Schad 2002, p. 80).

The situation loosely reminds one of college campuses when new lawn is laid down. Landscapers typically wait to see where human traffic creates clear pathways through the grass before "solidifying" the paths with concrete.

Moreover, "when blood vessels first start to form, the heart does not yet exist … early blood flow stimulates the development of the heart" (Schad 2002, pp. 82-83). Again, form arises from movement. Thus, the spiraling fibers of the heart muscle that help to direct the blood in its flow are themselves a congealed image of the swirling vortex of blood within. This kind of mutuality holds even for the heart's basic structural divisions:

> Before the heart 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 [4] (Holdrege 2002, p. 12).

For further examples, see Chapter 5, "Our Bodies Are Formed Streams".

Principle #5: CHARACTER

> ***BIOLOGY REQUIRES PORTRAITS OF SPECIFIC CHARACTER, NOT FORMULATIONS BASED ON UNIVERSAL LAW.*** *We have seen that an organism, as a focal center of its own unique way of being (Principle #2), cannot be understood biologically by means of the kind of universal law or causality we currently look for in the inanimate realm. Our understanding depends, rather, on principles that stand above physical cause and effect in the hierarchy of explanation and understanding — principles of organization and coordination, of intention and purposive direction, of meaning and self-realization. So how do we understand an organism? Through a kind of portrait. Just as we gain our deeper understandings of an individual human being by means of insightful biographies, not notions of physical determination, so we must try to understand any species or individual organism by building up an insightful picture of its character. A portrait, of course, is always aimed at bringing out the interior dimension of a more or less individuated subject, whether that subject is a species or an individual human being.*

An organism's nature is all about qualitative performances testifying to its own, specific way of being. It is about a distinctive *character*. It requires from us a recognition we can only describe as "holistic". During the last century the Cambridge University zoologist and member of the Royal Society, C. F. A. Pantin, offered examples from his own experience as a basis for understanding what sort of reality we are trying to apprehend when we are attempting to identify an organism — that is, when we want to recognize it for what it is. He said that recognition in the field "seems to depend on the whole available impression":

> Even a statement such as "The spines of the sea-urchin I am looking for have something of Chippendale about them — whilst that one looks Hepplewhite" may be significant. And if, when we are collecting [the planarian flatworm] *Rhynchodemus bilineatus* together, I say,

> “Bring me any worms that sneer at you,” the probability of your collecting the right species becomes high.

A naturalist who is intimately familiar with a given species will recognize it using very different cognitive faculties compared to the novice who is using an identification “key” consisting of a set of yes-or-no questions relating to isolated features. Because the whole impression is an impression of the whole, it does not arbitrarily force us to discard the greater part of what we can recognize in the organism. By contrast, as Pantin observed, once we have run through a key’s list of yes-or-no features, “a very great deal of the impression which the organism makes upon us still remains ‘unused’. This residue is undoubtedly important in our recognition of species even though it cannot be analyzed in just this [yes-or-no] way” (Pantin 1954).

To use an example given by the philosopher Ronald Brady: you find yourself engaging in one sort of activity when trying to recognize an old friend in a crowd, and quite a different activity when struggling to identify a stranger in the same crowd by proceeding through a list of discrete features (Brady 2002). You already have an overall impression of your friend — one perhaps sufficiently rich in its expressive potential to enable nearly instantaneous recognition of him even in postures or activities you have never witnessed before. As you scan the crowd, there are countless possible gestures of form or movement that might tip you off to the presence of the person you are looking for. Each one of them bears, not some literal and specific, easily definable feature, but rather the expressive signature of the friend. That is, they are all shone through by the same qualities, the same unifying character — a fact demonstrated by your ability to recognize numerous outward, novel manifestations as expressing the way of being of one individual.

In the analytical approach, by contrast, you are reduced to identifying, one by one, a set of low-level features described in unexpressive and rather more literal terms. Given a set of successful recognitions, you say, "This must be the person" — but you still do not recognize him in the way you would a friend. Time and familiarity are required before you can experience the inner, expressive unity that raises the particulars into a coherent and multi-dimensioned whole.

It’s also worth noting that an error in qualitative recognition ("For a moment I thought you were your brother") is less clear-cut than an error in applying an identification key. In general, Pantin suggests, there is truth in qualitative misjudgments. We were not altogether wrong. The mistaken impression was more or less like the thing we were after. "You really do look a little like your brother. In taking you for him, I was truly recognizing in you certain aspects of him". We do not have neat, yes-or-no judgments so long as we are reckoning with the qualities of living things.

So it is hard to be altogether and absolutely wrong when assessing the character of an organism. It is more a question of the depth or superficiality of insight, the fullness or vagueness of the depiction, the artistic adequacy or obscurity of the sketch. This truth has come to the fore today in genetics, where movements, rhythms, and contextual “portraits” of the overall current cellular state turn out to be essential to our understanding of the function of specific DNA sequences.

For some wonderful examples of scientifically informative "portraiture" in biology, consult the whole-organism studies in Holdrege 2021, and also the various articles at Whole-Organism Biology: A Goethean Approach on the Nature Institute's website.

Principle #6: SELFHOOD

> **UNDERSTANDING THE HUMAN SELF REQUIRES US TO DISTINGUISH OUR OWN INNER ACTIVITY FROM ITS PRODUCTS.** *We observe in ourselves a distinction between all our interior contents, on one hand, and the activity of our own selves from which some of those contents originate, on the other. For example, we can distinguish between thoughts already achieved (which we may recall from memory without having to repeat the original thinking), and the acts of thinking that first gave rise to those thoughts. Our ability, as subjects, to undertake an inner activity as our own and to make its products into subsequent objects of our attention is a mark of our selfhood and our individuation as human beings.*

Owen Barfield was making precisely this distinction when he remarked that the break between the human self and the not-self does not occur at the physical boundary of the skin. It is, rather, "the break between the act of thinking and the product of thought … The more, therefore, my thinking is my own act and the less it is mere 'externally' induced, passive reverie, by that the more am I an independent and responsible self" (Barfield 1977, p. 163).

Our thinking as self-conscious individuals — when we are truly *thinking* and not merely free-associating or rearranging old thoughts out of habit — is our own act. We can also say of our perceptions (so far as they are informed by thinking) that they are, in part anyway, our own acts. But this is not to deny that most of our perception is informed by thoughts we first had as children, or as students, or in any case prior to our present perceiving and responding to the world. This is a practical necessity; we could hardly function effectively in life if we had to produce afresh, moment by moment, the thinking appropriate for bringing to meaningful appearance every detail of our raw "sense data". (See in Chapter 13 the discussion of persons born blind who had their sight restored later in life.)

So the greatest portion of our interior life, at this stage of our evolution anyway, is unavoidably governed by habit. And this in turn points us back to all that we have received, and continually receive, often without consciously reflecting on it, from our natural and human surround. Beyond perception, we can ask how much of *all* our interior contents are "things already become" rather than expressions of our individually willed, originative activity. Not only things passively perceived, but also mental pictures, fancies, memories, dreams, reveries, automatic associations, old trains of thought — these fill our minds, and often serve for most of our interior life, quite without any genuine creative activity.

How much of our inner life comes from "outside", so to speak — for example, from our immediate family environment or the wider culture? Whether I am approaching a red light while driving a car, sitting in a corporate work environment, attending a baseball game, or casting a vote in a public election — in each case I orient myself by means of entire worlds of thought and habit constituting elaborate contexts of meaning I scarcely need to take conscious note of. Within each different context I find myself in a markedly different "mental place", ready to fit myself into the interior shape of the context — and this without any need for much of a fresh effort of thinking.

And yet — crucially — even the conscious or unconscious contents we "soak up" from our environment — contents we cannot claim as products of our own activity — have an interior-originated character. The most tiresome cliché of speech and thought we rather mindlessly toss off was once, in someone else if not in ourselves, a fresh and perhaps deeply insightful turn of phrase. Whatever can live in us as an inner content must have originated from inner activity. And, as I have been pointing out all along, the material world itself is an expression of interiority.

Quite apart from old habit, we are always at least potentially capable of those lucid moments of inner ("spiritual") activity we can call our own. And, among the range of organisms on earth, we seem to be alone in this. How much grief comes from trying to understand the awareness of simple organisms as if it were like our own creative *activity* of thinking!

At the same time: how much grief comes from refusing altogether to see the play of meaning, thinking, and intention *through* the organism — through the perhaps dream-like and "enchanted" flow of its awareness![5] But this is a matter for us to consider only alongside the principles to follow.

Principle #7: Nonselfhood

Organisms in general lack human-like selfhood. *Given our powerful tendency toward anthropomorphic thinking, it may be that we can best understand earlier-arriving species, to begin with, in terms of what they lack. They lack anything seriously resembling a human self. We cannot assume that they have anything very much like our own sort of self-awareness or ability consciously to plan, organize, and pursue goals. In terms of Principle #6, they do not make thinking their own act. As we will acknowledge, however (Principle #9), this does not prevent them from living thought-full, well-directed, and meaningful lives. It remains true that their interior dimension is the primary basis for our understanding of their lives.*

Once we have distinguished between an activity of a self-conscious being and the products of that activity (Principle #6) — a distinction we can easily observe within ourselves — we can see how an organism might possess a non-self-aware form of inner life. It can be a vessel for thought and thinking that is not its own as an individual organism, and without being an original thinker in the human manner. And we can imagine this to be true in a yet deeper sense of all inorganic phenomena. It is for us, as humans, to investigate what we can do to bring the thinking in all phenomena, organic and inorganic, to conscious, active, and creative reality within our own experience, which is our participation in the creative activity through which the world is sustained (Chapter 24).

So we can say that some of the character of other organisms is accounted for by what they don't have — namely, a human-like capacity, as self-aware individuals, to carry out acts of thinking, imagination, and willing that are fully and intentionally their own. For example, they do not formulate well thought-out goals and then exercise a conscious resolve to achieve them. This is true despite the fact that their lives, too, are thoroughly end-directed, often in creative and persistent ways. But as for *conscious* planning capacities the individual organism can call its own, virtually all biologists would rightly say that non-human organisms do not come close to equaling our own abilities in this regard.

Yet the relation between humans and other organisms seems to be a tortured topic for many biologists. For example, they see humans as close relatives of certain primates, and are fond of referring to "humans and other animals" — as if to curb any unfortunate tendencies we might have to claim a high or special destiny for ourselves.

But in other contexts those same biologists are often tempted to "wall off" our human interior capacities — perceiving, cognizing, thinking, willing, imagining — as if they were alien to the larger story of evolution and irrelevant to the functioning of all those nearer or more distant relatives of ours. So humans become both "mere" animals on one hand, and bearers of high, "unnatural" capacities threatening science with dreaded incursions of Spirit, on the other.

The problem here is that many researchers find it impossible to make a proper distinction between human interior capacities and those of other organisms without denying the interior — the thought, intention, and intelligence — of other organisms altogether.

There is a rapidly growing literature today on the role of agency in the life and evolution of organisms. In this literature, a disavowal of *anything like* human agency, as if it would automatically introduce an unnatural element, is almost a cliché. So it is that, in an otherwise valuable article on "What We Can Learn from a Biological Agency Perspective", three of our most insightful commentators on evolutionary and developmental biology offer the obligatory disclaimer that agency in non-human organisms is not "an 'intellectual' phenomenon":

> Ascribing agency to a system in no way imputes to it intentions or desires. The association of agency with mindedness is understandable, but nevertheless misguided. To be sure, the cognitive and conative [volitional] capacities of humans are paradigms of agency. But thinking is an extremely sophisticated, rarefied form of agency. Genuine agency is manifest in any living system that is capable of responding adaptively to its conditions, including unicellular organisms (Sultan et al. 2022).

That is well and good as far as it goes — and sounds like much of what I have been saying above. But there is no discussion in the paper of *what is required* for those adaptive responses (which rocks certainly don't have) or for the agency of organisms in general. More particularly, there is no mention of the *non-self-aware* ways in which *something rather like* human mindedness, cognition, and intention must operate in non-human organisms capable of exercising a profoundly wise and competent agency. This is a startling omission if indeed, as the authors claim, the "capacities of humans are paradigms of agency".

Certainly the thinking self (Principle #6) does display, as the authors say, an especially sophsticated agency. This agency, as I have been pointing out, is associated with our ability to make thinking our own act. But we can distinguish humans from other organisms in this way without introducing unjustified assumptions into the distinction. I mean, for example, the gratuitous assumption that no sort of interiority, no intelligence or wisdom — no significant and guiding imagery taking, for example, the form of cognitive perception, however dulled and dream-like — can play through non-human organisms.

Not even those who set human inner capacities apart as "unnatural" and who fear that those capacities might contaminate our understanding of other organisms are relieved of the responsibility to conceive the effective agency of those organisms *somehow*. The setting aside of our own self-aware capacities in no way justifies an effort to understand the agency of other organisms without referring to forms of intention, willful striving, perceiving, and the capacity to recognize meaning in the surrounding world. ("Are those dimly lit, half-hidden, motionless canine forms in the distance a real threat, or not?" — the question *needs* to be answered intelligently.)

When our pet dogs and cats are looking at something and assessing how to respond, they are surely not *reasoning* like humans. So, then, what *are* they doing in their perceiving and assessing? The question deserves a frank attempt at an answer from biologists. And there is no answer in the often implied assumption that organisms are like machines (Principle #3).

Those who take the machine as their model always seem to forget that a real intelligence — that of the machine designers and builders — certainly is at work in the machine. But it does not inhere in the materials of the machine, all the way down to the molecular level. Rather, it consists in the externally imposed arrangement of parts. Those who rely on machine models are the ones who contaminate their understanding of other organisms with their own thought-full interiority — and they do so in a way that ignores the fully immanent wisdom of those organisms, which, unlike in machines, manifests at the very roots of their material being and precedes the differentiation of material structures.

We need to distinguish other organisms from ourselves with care, and without drawing absolute lines for which the evolutionary record gives no justification. Our own "paradigmatic" lives would have provided an easy starting point, since only part of our inner activity belongs to our true and innermost self. The rest, in all its organic unconsciousness and material (physiologial) effectiveness, and with all its relevance for other organisms, also needs to be accounted for by biologists.[6]

We will explore problems related to this in the next few principles.

Principle #8: Consciousness

THERE EXISTS A WIDE SPECTRUM OF CONSCIOUSNESS IN ORGANISMS. *We must think of the unconscious, rather paradoxically, as "consciousness that is not conscious". That is, the unconscious takes its place within a vast range of possibilities of consciousness. In humans, unconscious contents can potentially rise to consciousness, just as*

> *conscious contents can fall into the unconscious. The boundary is extremely porous. No one who is reasonably self-aware can doubt that a good part of the very real meaning and motivation of his behavior is less than fully conscious (even if it may be consciously recognized as such at some later time). This suggests that unconscious contents can in some ways function much like consciously thoughtful and volitional activity.*

When a pianist plays a Beethoven sonata, the infinitely complex movements of her fingers, arms, and whole body must somehow express her intentions. On any particular occasion — say, a funeral or wedding — she may inflect her interpretation so as to yield a slight shift of character and mood. This means she will modify all those complex movements in an almost unthinkably nuanced manner, appropriate to the meanings of a particular context.

The result is an utterly refined physiological realization of her intentions, all the way down to the finest details of gene expression. These must vary, for the sake of the performance, from one cell to the next over trillions of cells. And, as I have documented in earlier chapters, there are countless other cellular activities that must proceed in harmony with the performer's intentions — activities that include those 300 or so cooperating molecules in each of the many spliceosomes per cell, carrying out the intricately end-directed work of RNA splicing (Chapter 8). That is, all those molecular processes must *themselves* become expressions of the meanings of the context, whether it be a wedding or funeral.

It's hard to deny the recognizable character of thought, will, and intention along the entire spectrum of consciousness, and we have no reason to think the continuity disrupted anywhere between our fully conscious intentions and the cellular processes that yield with absolute seamlessness to our higher activity. In particular, we do not find any break between the pianist's conscious effort to realize her expressive intentions, and the unconscious expression of those intentions at the molecular level. Every cell of her body is *informed by* her thoughts, feelings, and intentions — this despite the fact that no cell thinks, feels, or intends in any way we would want to call "self-aware".

Quite evidently, then, our cells possess their own meaningful sort of inner life. Whether they are replicating their DNA, or dividing, or dealing with a viral infection, they show themselves to be capable of end-directed, purposive behavior. This is consistent with their lending themselves so naturally to being informed by the pianist's intentions. And yet nothing in this picture requires us to imagine our cells thinking and willing as their own act (Principle #6).

The widely embraced "psychosomatic" view of the human being is relevant here. It's not only that cancers, heart disease, peptic ulcers, and other ailments correlate to one degree or another with stress, personality type, or psychosocial circumstances. The effort to distinguish purely physical from psychosomatic disorders is widely viewed as obsolete, since it is now difficult to find any physical illness whose onset, course, and treatment (think of the placebo effect) are not influenced by interior, or psychic, factors. And many of these factors are a long way from being our own self-aware, conscious acts.

There is another approach to the spectrum of consciousness. Whatever process it was by which the original communal consciousness of our ancestors became individuated — by which it gave way to the modern self-consciousness of the human individual — we can be quite sure it was indeed a process, perhaps a long and slow one. Would anyone want to suggest that there was some boundary in time, clear-cut or otherwise, before which individual authorship of our own inner activity was wholly absent, and after which it did exist? Did the individuated human being, possessed of self-awareness, just appear "out of nowhere"? But if the emergence of selfhood was in fact a gradual evolution, we can most easily imagine it as involving a slowly changing balance between those contents lying in the subconscious (or collective consciousness?) and those accessible to the self-aware individual.

Non-individuated communal consciousness, pretty much by definition, is a consciousness *in which one lives* without its being one's individual act, and without its being something one *attends* to in self-awareness. In other words, seen from the stance of our current self-awareness, non-individuated consciousness would have been more like a form of unconsciousness, or dreaming. And it wouldn't take an overly vivid imagination to extrapolate such primitive human communal consciousness backward in time, and through presumably radical qualitative changes, until one arrived at still less individuated instances of communal wisdom and intention — a wolf pack, a flock of birds, a school of fish, a beehive, a bacterial biofilm, or the way of being exhibited by any single species.

Thinking and intention in general, especially in their less conscious forms, seem to have an irreducibly collective aspect — or, at least, we can say that thinking and intention, in their immateriality, are not respecters of physical boundaries such as the skin of bodies or the membranes of cells. Just as the intentions of the pianist can orchestrate trillions of cells, each with their own, relatively independent life, so also the intentions making a unity of a wolf pack take appropriate form in each individual member of the pack during the subtle interactions of the hunt. The pack as a whole becomes an effective agent.

We have every reason to believe that the distinctive *ways of being* we recognize in every population, species, genus, family, and so on, are rooted in the (unconscious) thinking and intention playing through such groups. Whether it is one cell or many cells, a single organism or a community of organisms, *wherever we see the distinctive interior character of living performance*, we must ask what living agency is giving expression to that character.

We are in this way brought to our ninth principle.

Principle #9: Inner Life

An organism has its own sort of interior dimension. *Despite its lack of a human-like self, every organism makes of its life a wise and purposeful narrative reflecting its own, more or less centered needs, interests, and way of being (Principle #2). This implies, among other things, a power of perceiving and of responding intelligently to what is perceived. So, difficult as it may seem in terms of contemporary biological thought, we must consider an*

> *organism as having an inner (interior) life, however unself-conscious and different from our conscious human selfhood. It is hardly a truth difficult to observe: interior activities involved in perception, intention, intelligence, and purposiveness play through every organism all the way down to the cellular and molecular level, even if that organism is incapable of self-awareness or reflection upon its own interior contents. We can think of it this way: simpler organisms are more possessed by, than in possession of, the meanings of their lives — more caught up in them than originating them. Every organism, even the simplest one, is informed by the thoughts and intentions that define its character as a member of this or that species.*

In cutting down trees and building dams and homes, beavers perform work as elaborately intentional and purposive as one could ever hope to see. Similarly with termites constructing their intricately crafted mounds. But citing such examples almost seems foolish, since *all* growth, development, and behavior, so far as it is understood biologically rather than physically or chemically, is pursued in a vividly end-directed, or (as I have sometimes called it) *telos*-realizing, manner.

The bird building a nest is not *consciously* preparing for its unborn offspring. Yet obviously it *is* preparing for its unborn offspring, and I do not know how we can avoid accepting both statements. The first step to such acceptance may be to see that the bird is *possessed by* the wisdom that plays through it, rather than *possessing* it. It's as if its life is sustained by the voices of a larger wisdom — a wisdom originating from we know not where and communicated upon the eloquent currents of wind and sunlight, the ruling powers of day and night, and the compelling, because unreflective, meaning of songs, drumbeats, and alarm calls.

But this is hardly acceptable language in biology, and many readers, I suspect, will by now have riveted their attention on what will seem to them a decisive problem. Any sort of perceiving seems to imply a perceiver, and thinking a thinker. If an organism is not perceiving and thinking as an act of its own self, then who is responsible for the *activity* of perceiving and thinking that I have suggested "plays through" or "informs" the organism from its larger environment?

We will take up the problem while considering a further principle:

Principle #10: MYSTERY

> ***A HEALTHY SCIENCE ACKNOWLEDGES THE MYSTERIES BORDERING ITS OWN UNDERSTANDING.*** *This is especially true when things we very well know insistently point us to gaps in our understanding. It is not wise to paper over such gaps or try to force our way into a mystery, whether by intellectual violence or by appeal to an authority we ourselves cannot fully underwrite, such as that of a person,*

> *philosophy, or religious tradition. But even without fully penetrating the mystery, we may find that the mere knowledge of its existence can have a wholesome and liberating effect on our understanding of nearby things.*

I do not have any clear or definitive answer to offer in response to the question, “Who is doing the thinking that plays out in the life of an earthworm or clam?” What I do want to offer is some indication of why I remain comfortable with the perfectly knowable things that (1) tell us this is a necessary question, and (2) give us some reassuring context for it.

There have been suggestions more or less aimed at our question. For example, there is the idea that spiritual beings act as “group souls” for different kinds of animals. But the first rule for our inquiry seems to me simple enough: don’t pretend to know about things of which you are ignorant. And the fact is, I have neither knowledge nor experience of spiritual beings acting as group souls of animals, and I never expect to have any such experience. So I am not particularly interested in even addressing the idea.

And that is just as well, since my main interest at the moment lies in illustrating the value of thinking *around* a difficult question in order to establish related things that one *does* know and to see whether this knowledge begins to make the question less mysterious. Then it can feel okay to leave the mystery alone and proceed further with what one actually knows, expecting that every additional insight will make a little clearer what *kind* of thing might possibly fill any remaining gaps of understanding.

So, anyway, drawing on much of what has already been said, here are a few brief suggestions about how we might move “around” the question, “If an organism is possessed by its thinking rather than being a self capable of making thinking its own act, how might we understand the thinking so clearly manifest in its life?”

This question, by the way, applies not only to animals, but also to humans before they became self-aware individuals — perhaps, for example, those humans living in the primary age of mythic consciousness (as best we can understand their minds based on the much later and no doubt distorted records that have come down to us either through literate cultures or through millennia of oral tradition).

- First of all, the idea that organisms are *informed* by a larger wisdom in which they are caught up is hardly a strange one in today’s biology. For nearly a century now biologists have demonstrated the need for some such idea by clinging to the severely problematic notion of the DNA sequence as a unique bearer of *information* that single-handedly accounts for the development, character, intelligence, and life of the organism. This is an attempt to reconceive the intelligence manifested in the organism as a whole, as if it could be said to have originated in a particular bit of well-structured material substance. Such a view is possible only when one forgets that material structure always arises from thoughtful activity rather than the other way around (Principle #4).

- More generally, the inner being of organisms is a fact biologists are increasingly finding it hard to escape. The focus by a growing number of researchers on intelligence and consciousness even in single-celled organisms and plants may, we can hope, become more discriminating, but it is not likely to go away, as opposed to becoming more insistent. Countless biologists, including many of the most prominent figures in the field, have conceded that organisms certainly appear to carry out lives full of perceptive, thoughtful, intentional, end-directed, meaningful performances — and yet are not selves in anything like a human sense.

Even a look backward through human history reveals an ever less individuated, ever more collective sort of mental condition (Chapter 23, “The Evolution of Consciousness”). So our question about the nature and source of a more collective and less self-possessed conscousness does not seem to be a crazy one. It seems to demand our consideration, and invites our attention even in our own most ancient literature. We saw in that earlier chapter on the evolution of consciousness how Homer’s characters naturally and unreflectively received some of their own agency from “outside” — at the hands of what they took to be gods and goddesses.

◆ We today have no grounds for ignoring the distinction between what is more conscious and what is less conscious, or unconscious (Principle #8). This distinction enables us to begin thinking about the inner lives of beings other than humans. These are beings who have not achieved self-awareness or selfhood, but nevertheless show clearly that their lives are a manifestation of interior processes that cannot be described in physical terms, as opposed to the terms of consciousness, or interior activity. This activity may not be their own in the human sense, but it is a real and ongoing activity nevertheless, for we see the meanings in terms of which it is framed.

◆ In the example of the pianist (Principle #8), we noted the continuity between the actively exercised intelligence of a self-conscious human being and the “organic” consciousness (or unconscious powers) at work in her body and cells. Here we have an example where the trillions of relatively independent but non-self-possessed cellular “organisms” constituting the pianist’s body participate harmoniously and collectively, and in a perfectly natural way, in her inner life — in her thoughtful and intentional activity.

Surely there is a great difference between this and the wise intelligence through which the countless bacteria within a biofilm achieve a purposive unity. But there remains the general principle of collective participation in a larger governing agency.

◆ We do not consciously experience, at its source, our power to move our own bodies, and we have no idea how this actually happens. So, even in explaining our own conscious performances we must appeal to a working of inner powers other than what we can call “our own”. Whatever active wisdom ultimately thinks and moves in our own cells (and the bodies of other organisms, including single-celled ones) must operate at the roots of material causation and manifestation — as we, in our conscious selves, do not.

So we cannot in any case escape an unanswered question about the interior dimension of our own lives — one closely akin to our question about the earthworm and clam. Where does the inner activity come from through which our intended meanings impart appropriate gestural form to our own limbs?

◆ Further, all this gains a richer coloring when we take seriously the fact that the material universe already manifests its own sort of interior dimension (Principle #1). The question “Who acts?” or “Who thinks?” then becomes unavoidable and natural (if also sometimes perplexing) in almost every context of inquiry. Such contexts include inanimate ones where we cannot help recognizing conceptual order and ideal law, yet the origin of this order and law remains more or less completely hidden from our immediate experience.

- This coloring is deepened when we consider that our own language and thought, and therefore our self-consciousess and selfhood, represent a kind of in-gathering of some part of the world’s thoughtful aspect. In this way, the “speaking” through which the world comes to manifestation achieves a bright, wakeful focus in the human individual (Chapter 23, “The Evolution of Consciousness”).

- Given the previous point, we may perhaps be forgiven for imagining that the thinking at play in an amoeba derives from some part of that same thought-content of the world that has also come to an individuated self-conscious focus in ourselves. But in the amoeba’s case, this distant “dream” of light and understanding is not remotely near kindling into flame as a vivid self-awareness. As I put it in this footnote, every organism is a local blossoming of thought, even if not yet a thinking self.

In sum: the routine biological fact is that a single, unified, organizing intention can play through numerous physical entities, as it does through all our cells during the highly coordinated activity of development. This fact already covers much of the ground necessary for an answer to our question regarding collective intelligence and intention. One thing, at least, seems clear enough: there is in none of this any solace for materialist-minded biologists who can’t bring themselves to acknowledge the interior life that every organism so vividly presents us with. This interior life — and the taboo it lies under — seems to be the root problem for most biologists. Once the taboo is lifted, releasing the protected dogma of materialism into the free air of scientific conversation, the things we have been talking about here will not seem particularly remarkable.

Principle #11: Time

THE MYSTERY OF TIME IS CENTRAL TO THE LIFE OF ORGANISMS. *We clearly have little understanding of the nature of time, and this creates many difficulties in our efforts to comprehend the life of organisms. The study of embryology and development shows every organism to be a unity, not only because every part is informed by the coherent reality of the whole spatial organization, but also because every moment is informed by the pattern and character of the whole life cycle. We seem to have few intellectual resources for reckoning with this fact, which threatens to collapse — or transform — all our thinking about organisms.*

That bird I have spoken of, in its nest-building, clearly relates to time differently from us. It lives a “well-planned” life without planning anything, as if its future is somehow integral to its present.

We humans occasionally have a bare hint of this overcoming of separate moments of time. We have it, for example, in the experience of “flow” when an athlete, musician, or speaker “goes unconscious”, as we say, and becomes so intensely present in the moment that she seems to transcend it without conscious calculation or planning. Things just happen — and in an unusually effective way.

I believe that many Eastern and other wisdom traditions suggest the possibility of deepening this sort of experience by “entering into the moment” with such intensity that it becomes a kind of “eternal now”, bringing with it an ability to act out of a larger, trans-temporal unity. But whatever we make of all that, for the bird it’s as if it needn’t consciously *plan* for its offspring because the temporal unity of its life, way of being, and consciousness was never fragmented into separate moments in the first place.

It’s not difficult to see the unreality of the common idea of the present as an infinitesimally thin (and therefore effectively content-free) moving line dividing the past from the future. A comment I’ve seen attributed to the physicist David Bohm, but that I find it impossible to verify, is in any case significant: If the present is the point between a past that no longer exists and a future that doesn’t yet exist, it means that the present is a point separating two unrealities. It’s hard to make much sense of this.

Examination of our experience at any particular moment shows that our life in the present is not balanced precariously on an impossibly thin and insubstantial knife edge, but rather transpires within a broader, well-blended temporal context, with an emphasis (but hardly a sole emphasis) on the recent past and the prospect of the near future. Without such a present context of potentially unlimited breadth backward and forward, we would be “lost in time”, never knowing where we were amid the connections of events. We would never be able to relate meaningfully either to what has happened or to the possibilities for guiding events toward fruitful outcomes.

So, if only to a modest extent compared to the bird, our experience shows us living within a holistic, temporal tableau. Moreover, we can always try to expand the “presence” that holds together the near-past and near-future in our common experience. Perhaps there is nothing in principle to prevent this presence from being expanded more and more, until it embraces the remote past and the distant future. What would it be like to live in such a context? Perhaps very hard to imagine — but also very suggestive and fruitful. After all, we’re not talking about a possibility fundamentally disconnected either from our own current experience or from the life we observe in the bird.

There is another way we can recognize a necessity for overcoming the limitations of our current human experience of time. I have in mind our observation of movement in all its forms. For if we manage to see white clouds drifting across the blue sky, it can only be because we have experienced successive moments as a unity — as a single, unfragmented phenomenon. No collection of instants, each cut off from its “before” and “after”, would give us movement.

The same holds true for embryology, as suggested in the statement of Principle #11 immediately above. To talk about any process of organismal development is to recognize a meaningful whole unfolding in time. We can reflect upon such a whole only because the earlier moments are informed by the same larger meaning (which some might reasonably prefer to call an “archetype”) as the later moments. That is, the same meaning, the same lawfulness, playing through time, lends to the entire developmental process a single identity that we have no difficulty recognizing.

This does not imply a conscious "aiming at" a goal, but only a unity of meaning. Biologists have had great difficulty distinguishing between these two possibilities. The meaning, or archetype, at work in development might be understood as a "muscular organism of thought", a dynamic, generative idea capable of unfolding in time as the form of material substance.[7] We looked quite explicitly at such a generative idea in Ronald Brady's analysis of plant leaf sequences (Chapter 12).

Strange things happen when we start dividing time into discrete moments. The unity and meaning of things is lost, the seamless fabric of reality is torn.[8] And yet we must also recognize that the tear in reality between past and future is where our nascent freedom comes alive. This is where we are given an opportunity to pause, learn from the past, and apply that learning to our shaping of the future. We can insist on our own way, for good or ill and in truth or error, rather than be carried along by unconscious currents of life.

In our present stage of evolution, we have mostly fallen out of the time-unity of that bird's life. We have little choice but to consciously plan things. And so we assemble the disconnected moments of our lives in a pattern of our own choosing, rather as we spatially assemble the parts of a machine according to our conscious purposes. In both cases, our capacities might seem dreadfully artificial compared to the unmechanical life of a bird living each moment as an expression of the governing unity of its life. This artificiality no doubt helps to explain our ability to play the role of Destroyers on earth.

But there is real hope if only we can, in our freedom, recognize the unity from which we have been torn and the contrived nature of our current creations. Might we, in our freedom, eventually move beyond tinkering with things from without? And might we move beyond our isolation in the current moment, where we must plan our future while cut off from the wider intelligence that has nurtured all life on earth?

Whatever our answer to such questions, we must wonder how biologists can possibly pursue their science without at least acknowledging the doubt thrown over all their thinking by the problematic character of the human experience of time in relation to the living kingdoms as a whole.

Principle #12: A KEY

HUMANS ARE A KEY TO EVOLUTION. *Given that our bodies comprise vast and diverse populations of single cells, ranging from amoeba-like macrophages (white blood cells) to the various cells forming hard bone; given that our lives are deeply integrated with symbiotic microbes whose numbers match or exceed the number of our own cells; given the sophisticated developmental processes that carry us, in one lifetime, from a single-celled zygote to an exceedingly complex and balanced adult form; given the unique evolutionary achievement of our nascent selfhood (Principle #6), along with our*

> *consequent ability consciously to take hold of the thought-full and intentional interior of the evolutionary process and not merely be possessed by it; and given a human culture upon which all life and evolution on earth now depends, we are, you might say, the alpha and omega of the evolutionary story. What seems incontrovertible is that we represent the highest and furthest reach[9] of the thinking — which is to say, the ideas and meaning — taking form in evolving earthly life.*

There came a time in evolutionary history when life awakened, became self-aware, gained a voice, and began testifying to its own inner nature. The voice it gained was … *human speech*. Speech and thought. It is strange and ironic that we should step gingerly around these realities as if they were somehow spooky and unnatural. If they really were spooky and unnatural, it would be particularly remarkable that they are the very capacities through which responsibility for the overall meaning and direction of evolution is passing over into humans.

We are beings in whom evolution has brought to conscious flower some part of the wisdom and agency that was already at work in the simplest one-celled organisms. Can we fully understand any process of becoming except in the light of its fullest development? In any case, it seems elementary that we can comprehend evolution only because we are one of those organisms who, alone upon earth, can *see* evolution, and who can recognize it as having led naturally and step by step to our seeing.

In reviewing a book about the evolution of minds, Philip Ball, the always stimulating columnist for *Nature*, wrote that the book's authors placed an unfortunate emphasis on human minds. "The structure of a progression from the seemingly simple minds of bacteria and amoebas to the complex ones of primates", he said, "makes narrative sense, but recalls the outdated image of evolution with humans at the apex" (Ball 2022).

But perhaps we can be more interested in the truth than in what seems outdated (or trendy). And the truth is that the idea of residing "at the apex" gains a very different coloring when you consider that (1) we humans alone can empathetically recognize, somewhere within our own lives, the definitive way of being of every other form of life; and (2) we alone, among organisms on earth, are able to give full and explicit voice to the needs and interests of all the others.

Further, it is widely accepted that in our day we are witnessing an evolutionary transition whereby the intentional human mind is becoming the primary agent of evolution. This suggests not only a need to recognize the "apex" nature of our minds, but also to accept the ethical responsibility for all life on earth that this implies. (I doubt whether anyone would attribute ethical responsibility to any creature beside humans.) And, moreover, the transition tells us that the ongoing evolution, or self-transformation, of the human interior (that is, the evolutionary agent's work upon itself) is now the primary task and achievement of evolution. The burden lying upon us is a heavy one.

If our own interior capacities constitute a growing power consciously to direct evolution toward the future, then we have every reason to suspect that the interior capacities so clearly manifest in every unself-aware organism have likewise given expression — albeit unconscious expression — to the driving agency at work during earlier stages of evolution.

The inner life of nature that comes alive in our self-awareness can hardly be fundamentally different in kind from the wisdom that streams to and through the cells of our bodies (Principle #8). Actually, it's not clear how we might even speak coherently about the presence of *fundamentally disconnected* wisdoms (or intelligences, or thought-worlds) at play within the unity of an organism or, for that matter, the unity of the cosmos. There is no idea or thought-complex that is absolutely alien to, or cut off from, any of the meanings finding expression in the entire realm of ideas.[10]

Yet we still need to hold on to the distinction between thinking as *my act*, which becomes the basis for my human-like selfhood and consciousness (Principle #6), and the thinking that works on and through me (Principles #7, #8, and #9), but is not "my own".[11] Here it is important to acknowledge the limits of our own powers of selfhood. Our creative thinking has not evolved to the point where it can consciously take hold at the root of material manifestation. Of course, we do move our own bodies. But we don't know *how* we do so, or with the aid of what unconscious processes. At the same time, we know of no limit upon our evolutionary potential to continue expanding our sphere of intentional activity by raising unconscious processes to consciousness, where they become our own responsibility.

As far as it goes, our distinctive human consciousness can be seen as the highest achievement of consciousness on earth to date. But it is also, in another sense, a form of interior life not yet equal to the unconscious wisdom possessing the simplest one-celled organism. We humans certainly have room for a further evolution of consciousness!

What is certain is that we have been given the miracle of our own self-aware understanding, through which we can begin to understand other organisms — their inner life, their embodied way of being, and their evolution. And so we have the privilege of discovering ever more fully the connections, not only between our highest functioning and the intelligence of the cells in our bodies, but also between our own minds and the entire, far-from-mindless creative drama of life on this planet.

Notes

1. If the essence of science is the resolve to stick close to facts, then an acknowledgment of human agency — and, by extension, the agency of all organisms — is much closer to the spirit of science than the denial of any meaningful agency. That is, it sticks closer to the reality of experience. The old idea, still in force within the reigning scientific imagination, that we need to start our analyses with little (falsely) imagined billiard balls and then build up from there, rather than starting with direct experience, is where the trouble arises. The influential, early twentieth-century French philosopher, Émile Boutroux, expressed the key idea in a 1911 address to the Fourth International Congress of Philosophy in Bologna, Italy, in which he defended the claims of philosophy relative to science:

> Can we not, giving up to science everything in the nature of explanation, the reduction of this to that, fix ourselves resolutely on the ground of pure experience, and endeavour to show that, like science herself, philosophy aims at unravelling real facts: facts, moreover, which only differ from those which science studies to the extent that they are more primitive, less mingled with explanatory concepts and hypotheses, more strictly conformable to the idea of fact — of immediately given reality? Philosophy [presents] in a high degree, the essential characteristic of every science: belief in fact, in experience. Philosophy would then be an original and immediate experience, while science would be the systematisation of that common experience which is secondary and indirect (Boutroux 1912, p. 109).

2. On problems with the machine model of organisms, see Chapter 10 ("What Is the Problem of Form?").

3. Consideration of the distinctive nature of organisms often brings one back to Immanuel Kant and his *Critique of Judgment*, written toward the end of the eighteenth century. In this work Kant spoke of organisms as "natural purposes", because they are "*organized* and *self-organizing*" beings. An organism's parts, he observed, "so combine in the unity of a whole that they are reciprocally cause and effect of each other's form" — that is, an organism's parts (or organs) are always "reciprocally *producing* each other", and doing so within the dynamic unity of a whole (Kant 2000, II.1.65).

Kant, as a child of the Enlightenment, had a hard time taking his own words about natural purposes in a straightforward manner, and his peculiar way of approaching the entire subject lent support to the ambiguous modern habit among biologists of thinking that organisms somehow behave only *as if* they were purposive beings. But it has never been particularly clear how organisms in general — apart from human beings in their more deceitful mode — can behave *as if* they had certain capacities without actually *having* those capacities.

4. The twentieth-century American philosopher, Susanne Langer, clearly grasped the essence of the matter in her own discussion of the heart's development and functioning. The heart, she said,

> begins to form early in embryonic life, apparently serving no purpose until the incipient vascular system is ready to act with it. In the earliest phases, however, a characteristic function of periodic contraction, the so-called 'pulse,' appears in many evolving tissues, some of which will cease to exhibit it later, while others will join the cardiac development, so their rhythms will become entrained by larger ones and finally by the [entire] circulatory pulse.

This preliminary beating, which comes early in the heart's formation, "illustrates a basic characteristic of organic function, namely, that its integated activities are often detectable before their special mechanisms have even begun to appear". This is a powerful reminder that, in an organism's development, the part "descends from", or is differentiated within, its larger context, which is ultimately the whole organism. Speaking further of the heart's development, Langer wrote:

> Nothing could demonstrate more aptly the primacy of acts in biological existence, and their gradual concentration in those regions of an organism where they can expand, dominate and integrate most fully. This order of development, from differentiating function to

> specialized location (tissue determination) and finally specialized form (cell determination), has been noted many times by embryologists. [American zoologist] Charles Manning Child remarked, fifty years ago, that “differences in reaction or in capacity to react very commonly exist in different parts even before visible differentiation occurs, or in cases where it never occurs.”

Langer reinforces these remarks by citing the embryologist and author of *Form and Causality in Early Development*, Albert M. Dalcq, to the effect that, to begin with, the unity of the nervous system “is not so much spatial as functional … The nervous system does not really originate from a unique and continuous layer of cells.” And the American developmental biologist, Clifford Grobstein, whose life spanned much of the twentieth century, concluded from his experimental studies of development in young embryos that “when nervous tissue ‘self-differentiates’ … the cells themselves have not yet acquired fixity of type as nerve cells. … some stabilization at the tissue level seems to precede stabilization at the cell level” (Langer 1967, pp. 200, 401-2).

For a more recent discussion of the heart, see the impressive evidences and analysis in Branko Furst’s technical treatise on *The Heart and Circulation: An Integrative Model* (Furst 2020).

5. We might think of this awareness — say, in a bison or alligator — as less a matter of clear concepts than of significant, directive (and sometimes compelling) feeling and image. But such a “dream life” can presumably vary without limit in vividness and distinctness, and we are hardly in a position to imagine its reality in organisms other than ourselves.

6. The University of Chicago legal scholar and philosopher, Martha Nussbaum, has written a stimulating piece in which she points to the various ways in which we discover intelligence, thoughtfulness, feeling, culture, and learning in other organisms. She recognizes that all organisms, including humans, need to be understood in the terms of their own lives, their own sort of striving and flourishing. But in her valuable effort to deny the wrong sort of distinctiveness to humans, she unnecessarily denies what does set us apart — which happens to be the aspect of our being that enables us to understand and protect other species.

Nussbaum refers to “the false lure of metacognition: the idea that reflexive self-awareness is the be-all and end-all of intelligence, and that we humans are unique in possessing it”. She says, in this regard, that “any creature who is capable of deceiving another creature is capable of metacognition, since to deceive you must be able to think about the mental state of another. Dogs, squirrels, many birds, and no doubt a long list of other animals have this ability, which is crucial to survival when you have to hide your food where your competitors won’t find it” (Nussbaum 2022).

But why must we take a dog to be “thinking about” the mental states of other animals in anything like the way *we* would do such thinking? This is a good place to notice how easy it is to ignore the difference between being a vehicle for the manifestation of thoughtful behavior, and being in the fullest sense the author of one’s own thinking.

I suspect that just about any practical sort of thinking humans engage in is, in one way or another, reflected in other animals. This is true even of the research about human infant intelligence. We can certainly observe a remarkable intelligence in infants — maybe in some ways a much higher intelligence than anything an adult can consciously lay claim to. (We could make the same comparison between an animal's intelligence and our own.) But this intelligence is not yet the child's own. It is more like the intelligence of its material and immaterial surroundings — or perhaps we should say, the "trailing clouds of glory" — from which the child progressively draws down its own conscious faculties. (See Chapter 23 on the evolution of consciousness.)

The fact that your dog engages in deceitful activity does not mean it could say to itself in its own dog language, "I think I will pull off a trick". In fact, most would agree that it never even says "I" — although it certainly possesses an *effective awareness* of itself as distinct from other dogs. Just as it most definitely "knows" it cannot jump over a house, it also "knows" that there are other dogs that are not itself. But this does not amount to anything like the potentials of human self-awareness. Your dog might *smell* a truth that you would summarize as "Oh, that's the neighbor's Rex". Its knowing this reflects a kind of thought or intelligence at work. But the dog does not *have* anything very like your sort of thought, "Oh, that's the neighbor's Rex".

I will have more to say about all this in discussing the following principles. But the crucial thing now is to hold in mind the distinction between the wisdom that plays through us, and the thinking that represents our highest being and is our own act, however infrequently we resort to it.

7. The common conviction among biologists that a term such as "archetype" is somehow mystical or tinged with the occult seems to result from forgetting that all scientific understanding takes the form of ideas. When one forgets this, then any explicit mention of ideas as playing a causal role in nature makes one think that some sort of occult force is being invoked. But in fact the "archetypal" nature of an organism is no more occult or mystical than the laws of physics, even if organic and inorganic ideas both require a method of recognition appropriate to their character.

8. Our fragmented notions of time, whereby each discrete moment of time is thought to contain the cause of what happens in the following moment, may be a serious obstacle to finding our way to holistic clarity regarding matters of causation. Barfield (1963, p. 175) once tried to provoke reflection about the puzzle of time and causation by means of a fictional dialogue between a school teacher ('A' in the following) and a particularly open-minded physicist ('B'):

> A: Does an effect follow its cause in time, or is it simultaneous with it?
>
> B: It follows; otherwise it wouldn't *be* an effect.
>
> A: I know it wouldn't. Is time infinitely divisible?
>
> B: We must assume so.
>
> A: I know we must. Then what happens in the instant of time that elapses between cause and effect? Alternatively, if we say they are simultaneous, how do we distinguish an effect from a cause?
>
> B: Aha!

The usual idea of scientific explanation by means of an appeal to causes and their effects has long been recognized as problematic by philosophers of science. And yet simplistic causal notions, not only within the general public but also among scientists, seem extremely resistant to change in any fundamental way.

9. There is something that grates on many people in words such as “highest” and “furthest” when applied to ourselves as humans. And it is indeed hard to be insensitive to the potential for an unseemly arrogance in these words. Yet we can also wonder whether some of the irritation the words arouse is driven, at least in part, by an uneasiness in the face of the burden of responsibility they would impose on us — responsibility, in the first place, for all our fellow beings on this planet who do *not* possess their own thinking, and whose welfare therefore hinges on *our* thinking. In any case, it is hard to bear well a high responsibility without first recognizing and accepting just how high it is.

10. Even thoughts that we think of as “absolute opposites” cannot be truly inharmonious or disconnected from each other, as shown by the fact that we routinely bring them into perfectly satisfactory relationship by means of unifying concepts such as *opposites* or *contraries*.

One way to approach the unity and interconnectedness of language is to consider the interplay between our hearing of particular words as we listen to speech, and our progressive apprehension of the overall meaning that more and more shines through those words, modifies their identity, and subordinates them to the developing direction of thought. Without the plasticity of words — without the “willingness” of every word to be brought into relation to any other word — coherent speech would be impossible. We could not understand speech without hearing individual words, but neither could we understand the individual words in their current meaning without grasping the overall import of what is being said — an import capable of informing all the words and uniting them in the larger meaning (Bortoft 2012).

The realm of language and thought is remarkably life-like. In any profound speech or text the words (or thoughts) exist in complex, organic, dynamic, and meaningful relations with each other. All possible words (or thoughts) are as if straining in this way toward living interaction with any and all other possible words or thoughts. It requires only a spark of imagination on our part for the relations between particular words to catch fire and throw unaccustomed light in new directions (Barfield 1973).

11. The thinking that is not “my own”, one might be tempted to say, illumines my cells “from outside”. This, however, suggests something machine-like, as if the thinking were coming to bear on cells like the thought of an external designer. But in fact it is a wisdom that expresses itself, as I have already suggested, at the very root of the organism’s material manifestation. It works immanently within, rather than externally upon, the organism. It constitutes every organism as a local blossoming of thought, even if not yet a thinking self.

Sources

Ball, Philip (2022). “A Tour of the Evolution of Minds”, *Nature* vol. 603, no. 7900 (March), pp. 221-22. doi:10.1038/d41586-022-00652-z

Barfield, Owen (1963). *Worlds Apart: A Dialogue of the 1960’s*. Middletown CT: Wesleyan University Press.

Barfield, Owen (1973). *Poetic Diction: A Study in Meaning.* Middletown CT: Wesleyan University Press. Originally published in 1928.

Barfield, Owen (1977). *The Rediscovery of Meaning, and Other Essays*. Middletown CT: Wesleyan University Press.

Bortoft, Henri (2012). *Taking Appearance Seriously: The Dynamic Way of Seeing in Goethe and European Thought*. Edinburgh UK: Floris Books.

Boutroux, Émile (1912). *The Beyond That Is Within and Other Addresses*. Pranava Books, India.

Brady, Ronald H. (1987). “Form and Cause in Goethe’s Morphology”, in *Goethe and the Sciences: A Reappraisal*, edited by F. Amrine, F. J. Zucker, and H. Wheeler, pp. 257-300. Dordrecht, Holland: D. Reidel. https://natureinstitute.org/ronald-h-brady/form-and-cause-in-goethes-morphology

Brady, R. H. (2002). "Perception: Connections Between Art and Science". Originally presented as an invited paper, “Perception and Hypotheses of Perception,” at a conference sponsored by the British Museum of Natural History (London, April 4-7, 2000). https://natureinstitute.org/ronald-h-brady/perception-connections-between-art-and-science

Brady, Ronald H. (2016; posthumous). “How We Make Sense of the World: A Study in Rudolf Steiner’s Epistemological Work”. https://natureinstitute.org/ronald-h-brady/how-we-make-sense-of-the-world

Furst, Branko (2020). *The Heart and Circulation: An Integrative Model*, 2nd edition. New York: Springer.

Holdrege, Craig, editor (2002). *The Dynamic Heart and Circulation*. The chapters originally written in German were translated by Katherine Creeger. Fair Oaks CA: AWSNA.

Holdrege, Craig (2021). *Seeing the Animal Whole — And Why It Matters*. Great Barrington MA: Lindisfarne.

Kant, Immanuel (2000). *Critique of Judgment*, translated by J. H. Bernard. Amherst NY: Prometheus Books. Originally published in German in 1790. Translation originally published in 1892 as *Kant’s Kritik of Judgment*. http://www.gutenberg.org/ebooks/48433

Langer, Susanne K. (1967). *Mind: An Essay on Human Feeling* vol. 1. Baltimore MD: Johns Hopkins University Press.

Nussbaum, Martha C. (2022). “What We Owe Our Fellow Animals”, *New York Review of Books* (March 10). https://www.nybooks.com/articles/2022/03/10/what-we-owe-our-fellow-animals-ethics-martha-nussbaum/

Pantin, C. F. A. (1954). “The Recognition of Species”, *Science Progress* vol. 42, no. 168 (October), pp. 587-98. http://www.jstor.org/stable/43415463

Schad, Wolfgang (2002). “A Dynamic Morphology of the Heart and Circulatory System”, in Holdrege 2002, pp. 77-97.

Sultan, Sonia E., Armin P. Moczek and Denis Walsh (2022). “Bridging the Explanatory Gaps: What Can We Learn from a Biological Agency Perspective?”, *Bioessays* 2021;100185 vol. 44, no. 1. doi:10.1002/bies.202100185