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1

How to Construct an Organism

> What I cannot create I do not understand.
>
> —Richard P. Feynman[3]

Not so long ago, newspaper headlines around the world proclaimed that scientists had created "artificial life." This astonishing news referred to an experiment from the laboratory of maverick molecular biologist Craig Venter, in which the DNA molecule of a simple type of bacteria had been artificially synthesized from its chemical building blocks (with some curious embellishments, like Venter's email address encrypted in the DNA's genetic code), and then inserted into a different species of bacteria, replacing that cell's own genome. Amazingly, this procedure resulted in a living bacterial cell that went on to divide and produce a colony of bacteria.[4]

Beyond its sheer technical wizardry, Venter's experiment seems to offer a unique insight into the nature of heredity—the transmission of biological information across generations that causes offspring to resemble their parents, and can thereby enable evolution by natural selection.[5] After all, Venter's research group had managed to decouple two fundamental components of a cellular organism—the genome (that is, the DNA sequence) and its cytoplasmic surroundings (that is, the immensely complex biomolecular machinery that constitutes a living cell). The resulting bacterial chimera, which combines the genome of one species with the cytoplasm of another, should therefore tell us something about the roles of the DNA sequence and the cytoplasm in the transmission of organismal traits across generations. Did Venter's

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bacterium resemble the species from which it got its DNA sequence, the species from which it got its cytoplasm, or both?

Reports on Venter's experiment emphasized the role of the genome in converting the bacterial host cell into a different species of bacteria: the genome induced changes in the features of the cell into which it had been inserted, such that, after several cycles of cell division, the descendants of the original chimeric cell came to resemble the genome-donor species. This result illustrates the DNA's well-known role in heredity: the base-pair sequence of the DNA molecule *encodes* information that is *expressed* in the features of the organism. Indeed, from here, it seems a small step to conclude that the cytoplasm (and, by extension, any multicelled body) is fully determined by the genome, and that the DNA sequence is all we need to know to understand heredity. Venter's experiment thus seems to provide a powerful confirmation of a concept of heredity that has underpinned genetics and evolutionary biology for nearly a century.

But take a closer look at Venter's experiment and the picture becomes less clear. Although many media reports gave the impression that Venter's "artificial" organism was created from a genome in a petri dish, the bacterial chimera actually consisted of a completely natural bacterial cell in which only one of many molecular components had been replaced with an artificial substitute. This is an important reality check: although it's now possible to synthesize a DNA strand, the possibility of creating a fully synthetic cell remains the stuff of science fiction.[6] In fact, rather than demonstrating the creation of artificial life, Venter's experiment neatly illustrates a universal property of cellular life-forms: all living cells come from preexisting cells, forming an unbroken cytoplasmic lineage stretching back to the origin of cellular life. This continuity of the cytoplasm is as universal and fundamental a feature of cellular life-forms as the continuity of the genome. Of course, cytoplasmic continuity does not in itself demonstrate that the cytoplasm plays an independent role in heredity. After all, the features of the cytoplasm could be fully encoded in the genes. Yet, the potential for a nongenetic dimension of heredity clearly exists.[7]

The continuity of the cell lineage has been recognized since the mid-nineteenth century but, since the dawn of classical genetics in the early twentieth century, many biologists have been at pains to deny or downplay the role of nongenetic factors in heredity, arguing that the

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transmission of organismal features across generations results more or less entirely from the transmission of genes in the cell nucleus.[8] Genes were assumed to be impervious to environmental influence, so that an individual could only transmit traits that it had itself inherited from its parents. These ideas gained prominence while the term "gene" still referred to an entirely theoretical entity, and long before molecular biologists uncovered DNA's structure and the genetic code. More recently, this view was popularized by Richard Dawkins in his memorable image of the body as a lumbering robot built by genes to promote their own replication. But this purely genetic concept of heredity was never firmly backed by evidence or logic. Venter's chimeric bacteria were foreshadowed by late nineteenth-century embryological experiments that combined the cytoplasm of one species with a nucleus from another species, providing the first hints that the cytoplasm is not a homogeneous jelly but a complex machine whose components and three-dimensional structure control early development. Further tantalizing hints of a nongenetic dimension to heredity were provided by the work of mid-twentieth-century biologists who discovered that mechanical manipulation of the structure of single-celled organisms like *Paramecium* could result in variations that were passed down unchanged over many generations. Today, after many more clues have come to light, biologists are finally beginning to reconsider the possibility that there is more to heredity than genes.

RETURN OF THE NEANDERTHALS?

Venter's experiment raises intriguing questions about the nature of heredity at the level of a single cell, but what about multicelled organisms like plants and animals? A single cell's cytoplasm is divided in half each time the cell divides and then supplemented with newly synthesized proteins encoded by the genome. It is this process of gradual conversion that allowed the bacterial genome to gradually reset features of the host cell in Venter's experiment. Can such conversion also reset the features of more complex life-forms?

Consider an example at the opposite extreme of the complexity gradient—the recent idea of resurrecting a Neanderthal. Some people believe that such a feat could be accomplished by implanting a synthetic

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Neanderthal genome (whose sequence was recently deciphered from DNA fragments extracted from ancient bones) into a modern human egg or stem cell deprived of its own genome. Ethical considerations aside, it would be extremely interesting to compare the physical and mental traits of our enigmatic sister species with our own, and on the face of it, such an experiment could be carried out by following Venter's recipe. What's less clear is how closely the resulting creature would resemble a genuine Neanderthal.

Neanderthals differed from us *Homo sapiens* in many features of their bodies, such as their muscular build, long, low skulls with heavy brow ridges, and more rapid juvenile development[9] (figure 1.1). Some paleoanthropologists also believe that Neanderthals differed from contemporaneous *Homo sapiens* populations in various aspects of their culture and social organization, such as their use of clothing, foraging techniques, and reliance on long-distance trading networks.[10] Which of these features could we expect to observe in an individual derived from a Neanderthal genome implanted into a modern human egg?

Clearly, such a creature would fail to exhibit Neanderthal cultural practices, since culture is not encoded in the genes (although a population of such creatures, if allowed to interbreed for many generations in isolation, could perhaps tell us something about Neanderthals' capacity to develop complex culture). A lone Neanderthal growing up playing video games and watching movies in its enclosure at the primate research institute would surely fail to develop many of the behavioral peculiarities of its species. Moreover, we know that physical activity influences the development of bones and muscles, while dietary preferences and practices (which are partly culturally transmitted) influence the development of dental and cranial features. So even the distinctive features of Neanderthal bodies may have been a product not only of Neanderthal genes but also of how they behaved and what they ate. A couch-potato Neanderthal will undoubtedly exhibit some of the distinctive features of Neanderthal physiology but might still end up looking more like a specimen of modern, industrialized *Homo sapiens*, with its proverbial joy-stick thumb, fondness for potato chips, and alarming body-mass index.

But the problem runs even deeper. In all complex organisms, development is largely regulated by *epigenetic* factors—molecules (such as methyl groups and noncoding RNAs) that interact with the DNA and

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Figure 1.1. Skeletons of a Neanderthal (*left*) and modern human (*right*). Can a Neanderthal be resurrected by implanting a Neanderthal DNA sequence into a modern human egg? (© I. Tattersall, Photo: K. Mowbray)

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influence when, where, and how much genes are expressed. Some epigenetic factors can be acquired through exposure to particular environmental factors such as diet, and can then be transmitted to offspring. Although recent research by Liran Carmel's lab in Israel has begun to uncover aspects of the Neanderthal epigenome,[11] it remains unclear which differences between Neanderthals and *Homo sapiens* were downstream consequences of genetic differences and which differences resulted from their long-vanished environment and lifestyle. Indeed, some epigenetic patterns found in children conceived during seasonal cycles of food shortage in an agricultural population in The Gambia in West Africa were also characteristic of Neanderthals, suggesting that these epigenetic features of Neanderthals may have been a result of their diet rather than their genes.[12] Unless such epigenetic factors, and other nongenetic influences on development such as cytoplasmic and intrauterine factors, can be reconstructed along with the Neanderthal DNA sequence, our Neanderthal may lose even more of its distinctive traits.

In short, we suspect that implanting a Neanderthal genome into a modern human egg would result in a creature that diverged in many behavioral and physical features from genuine Neanderthals. The reason for this is simply that a DNA sequence does not contain all the information needed to re-create an organism.

WHY NOTHING IN BIOLOGY MAKES SENSE ANYMORE

The idea that genes encode all the heritable features of living things has been a fundamental tenet of genetics and evolutionary biology for many years, but this assumption has always coexisted uncomfortably with the messy findings of empirical research. The complications have multiplied exponentially in recent years under the weight of new discoveries.

Classical genetics draws a fundamental distinction between the "genotype" (that is, the set of genes that an individual carries and can pass on to its descendants) and the "phenotype" (that is, the transient body that bears the stamp of the environments and experiences that it has encountered but whose features cannot be transmitted to offspring). Only those traits that are genetically determined are assumed to be heritable—that

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is, capable of being transmitted to offspring—because inheritance occurs exclusively through the transmission of genes. Yet, in violation of the genotype/phenotype dichotomy, lines of genetically identical animals and plants have been shown to harbor heritable variation and respond to natural selection. Conversely, genes currently fail to account for resemblance among relatives in some complex traits and diseases—a problem dubbed the "missing heritability."[13] But, while an individual's own genotype doesn't seem to account for some of its features, parental genes have been found to affect traits in offspring that don't inherit those genes. Moreover, studies on plants, insects, rodents, and other organisms show that an individual's environment and experiences during its lifetime—diet, temperature, parasites, social interactions—can influence the features of its descendants, and research on our own species suggests that we are no different in this respect. Some of these findings clearly fit the definition of "inheritance of acquired traits"—a phenomenon that, according to a famous analogy from before the Google era, is as implausible as a telegram sent from Beijing in Chinese arriving in London already translated into English.[14] But today such phenomena are regularly reported in scientific journals. And just as the Internet and instant translation have revolutionized communication, discoveries in molecular biology are upending notions about what can and cannot be transmitted across generations.

Biologists are now faced with the monumental challenge of making sense of a rapidly growing menagerie of discoveries that violate deeply ingrained ideas. One can get a sense of the growing dissonance between theory and evidence by perusing a recent review of such studies and then reading the introductory chapter from any undergraduate biology textbook. Something is clearly missing from the conventional concept of heredity, which asserts that inheritance is mediated exclusively by genes and denies the possibility that some effects of environment and experience can be transmitted to descendants.

In the following chapters, we will sketch the outlines of an extended concept of heredity that encompasses both genetic and nongenetic factors and explore its implications for evolutionary biology and for human life.

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