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WHAT IS A GENE? FROM MOLECULES TO METAPHYSICS

ABSTRACT: Mendelian genes have become molecular genes, with increasing puzzlement about locating them, due to increasing complexity in genomic webworks. Genome science finds modular and conserved units of inheritance, identified as homologous genes. Such genes are cybernetic, transmitting information over generations; this too requires multi-leveled analysis, from DNA transcription to development and reproduction of the whole organism. Genes are conserved; genes are also dynamic and creative in evolutionary speciation—most remarkably producing humans capable of wondering about what genes are.

KEY WORDS: Cybernetic genes, genetic identity, intentionality in genes, mendelian, molecular, searching genes

What is a gene? Answers have been changing. By some accounts we now understand genes better than ever (as we do atoms); by other accounts this understanding no longer finds the term useful (like vitalism). Over a decade ago, Petter Portin concluded:

> In a certain sense, now that genes can be isolated and analyzed biochemically in great detail by sophisticated methods, our understanding of the gene has become very concrete. At the same time, paradoxically, the concept of the gene seems to have become more general, open, and abstract. The very term gene seems to mean different things in different contexts.[1]

Scientists discover laws and regularities in nature; they also uncover the entities involved, such as kinds of atoms and their kinds of bonding. As science progresses, scientists get clearer about what they are studying. That gave us a new physics in the first half of the last century, when Einstein followed Newton. Spectacularly in the last half century, that has also been going on in genetics: figuring out the genetic code, sequencing the human genome, and tracking genes and their transformations.

Concepts are dynamic because scientists find out what was previously unknown. Older concepts will be used in new ways that align with the advances in the field; atoms are not uncuttable entities, but composed of electrons, protons, and neutrons. They can be split and

relativity theory illuminates the distribution of matter and energy in their splitting. Darwin transformed the concept of fixed species into evolving species. Older concepts may also be entirely abandoned: phlogiston and entelechy. Does "gene" any longer, in Plato's famous phrase, "carve nature at the joints"?

What is a gene? The answers considered here follow three stages, becoming ever more problematic, challenging, and revealing: (1) the Mendelian gene; (2) the molecular gene, with increasing puzzles about its specification; (3) the cybernetic gene, a multi-dimensional concept, at once pivotal and elusive. Throughout, I am a philosopher looking over the shoulders of geneticists, wondering how far a gene is objective in nature (like molecules), what kind of objectivity this is (molecular product storing information, emergent inheritance inviting metaphysical reflection). Or if "gene" is no longer as useful as before in scientific accounts, what in genetic accounts of evolutionary speciation and creativity does demand philosophical reflection?

Ultimately, there is a larger agenda: the nature of our human kind. Genes figure increasingly into our self-understanding, but mixedly. We do want heritage, roots—genetics in, with, and under us—but we do not want to be genetically determined, if we have too many "genes for" our traits. "Now we know, in large measure, our fate is in our genes." That comes with great authority from one of the discoverers of the genetic code, Nobel laureate James Watson, first director of the Human Genome Project.[2] But many geneticists demur: J. Craig Venter and over 200 co-authors, completing the Celera Genomics sequencing, caution that genetic "determinism, the idea that all characteristics of the person are 'hard-wired' by the genome" and accompanying "reductionism are two fallacies to be avoided."[3] Do not take a half-truth for the whole.

Genes also connect humans with animals, which is the reductionism issue in another form. Humans and chimpanzees have 98% the same genes (or 95%, the figures differ)—more precisely the same genes for forming proteins. We share 80% with rodents and 60% with chickens.[4] Genes for cytochrome c molecules are over a billion years old and widespread in organisms, from yeast to humans.[5] Obviously persons are not mice or chickens. But does revising the facts about shared genes revise our worldviews, make us more animal than we thought, and figure humans differently into natural history?

THE MENDELIAN GENE

Organisms breed, give birth to young, flower, and make seeds, transmitting their kind. They inherit structures and traits through lineages of individuals. Although some inheritance is non-genetic, as when geese learn migratory routes following older geese or fetuses inherit antibodies, most biological inheritance is by genetic reproduction. What passes from one generation to the next and determines the recurring biological characteristics of individuals and species? In 1866, Mendel spoke rather vaguely of "form-building elements"; others speak of factors; the microbiologists first saw chromosomes. But for a century the most common answer has been genes.

The contemporary word was coined by Wilhelm Johannsen in 1909,[6] from Latin and Greek roots for generate and giving birth. Some "seed" is passed from man to woman, from man and woman to child. Mendelian geneticists could see no genes but posited them by back-inference from the behavior of phenotypic traits. A Mendelian gene was the inherited locus that specified a trait (the color of peas). The novelty is that the units are atomic, discrete, specific characters, stable and independently segregating, something like atoms of inheritance. These functional units producing results in the life of the phenotype were also the segregating units of reproduction in heredity when through meiosis one generation produced the next.

Alternative traits were attributed to alternative genes, alleles, analogous to isotopes. A mutant produced a variant gene, evidenced in an altered phenotype, and such a variant gene continued to segregate as a unit, as before. There is characteristic similarity in form, function, location, enough to identify alleles as versions of the same gene, yet enough dissimilarity to term it an alternative form of the same gene. Geneticists also spoke of gene families. So classically there was already variance in these stable units of inheritance.

With the coming of microbiology, genes became units of inheritance lined up along a chromosome, like beads on a string. Some traits are linked; they tend to pass on together through meiosis because they are located close together on the same chromosome. Tracking this out enables gene mapping. So by the time of T. H. Morgan and *The Mechanism of Mendelian Heredity* (1915),[7] the term "gene" referred to some segment of a chromosome that produced a characteristic effect in the organism. These segments were more finely separated by tracking whether mutations were separated during recombination; if

not, they were on the same gene. The non-recombining mutant and the wild type were alleles of the same gene, not different genes. The frequency of separation, expressed in phenotypes, could be linked with the distance between genes on the chromosome, with calculated precision, expressed for example in centiMorgan units (cM).

Classical geneticists also knew that often one gene can affect a variety of characters (pleiotropy); also a single trait can be influenced by a number of different genes at different loci (polygeny). Most genes are also epistatic; they affect one another's effects. So geneticists had already found that genes were webworked, if they also believed that one gene produces one characteristic trait. But with a shift from genes as chromosome locations to molecular genes, this webworking was to become increasingly a problem.

THE MOLECULAR GENE

Chemists had dealt with acids and bases for over a century before molecular chemists were able to give a molecular account of an acid, involving hydrogen ions. Analogously in genetics, the molecular biologists were able to transform the Mendelian account; the gene became the physical region of the DNA containing the base-pair triplets that translated into the functional protein that produced the trait under consideration. The Human Genome Project provides this definition: A gene is "the fundamental physical and functional unit of heredity. A *gene* is an ordered sequence of *nucleotides* located in a particular position on a particular *chromosome* that encodes a specific functional product (i.e., a *protein* or RNA molecule)."[8]

Notice that there is "coding" and "function" in the definition. If so, the noncoding stretches of DNA, which is most of the genome, are not genes. The definition is also "particular"; one DNA stretch codes for one function—continuing the Mendelian gene, where one gene locus produces one phenotypic result, one gene, one protein or trait. One discovery that accords well with the classical segregating units is that there are start and stop codons. Further, the enzymes that cut and splice do not do so anywhere in the DNA sequence, but there are favored locations. This tends to confirm at the molecular level the earlier idea that there are segregating units that are at the same time functional units. To paraphrase Plato, these enzymes too need to "carve the DNA at the joints."

Nevertheless the Human Genome Project's concept of a gene has been increasingly upset during the last several decades. There are regulatory regions nearby (within 20-30 nucleotides) that also promote or suppress these starts and stops. Shall we include these and call the unit an "operon"? Such promoters, enhancers, and operators may also lie thousands of base pairs "up" or "down" the DNA being read.[9] Although not "read" for protein assembly, we can also term these "regulator genes."[10] Some genes make proteins; others regulate; many serve mediating functions, like a middleman in a market.

Some genes produce adult traits. Some are for embryonic development. Some are for transcription into nonmessenger RNA, regulating the production of the protein products. Even some unknown sequences we can call "genes," perhaps under the suspicion that these will later be found to have, or have had, functions. Gene needs a modifier to be more precise: " _____ gene." There are simple genes, complex genes, nested genes, assembled genes, transposable genes, molecular genes, populational genes, and so on. There are split genes, with DNA sequences used (exons) and DNA sequences cut out (introns), constitutive splicing (joining all exons), and alternative splicing (differentially joining the exons).

The complexities continue. There is gene overlapping. The output depends on differing reading frames of the same DNA sequence. Or the same output can be alternatively spliced. With changing environmental demands, the organism can shift the regulatory mechanisms, reading the same stretch of DNA, but splicing it differently to make various proteins, and employed for different functions. The DNA can begin to look like pieces in a Lego kit used this way or that, depending on the circumstances of the organism.

There are moveable genes: transposable bits of DNA can be excised and relocated on the same or another chromosome. There is polyadenylation: adding multiple adenine nucleotides at the end of transcription. Pseudogenes are similar to genuine genes but not transcribed because they are somehow broken. Contrary to the Mendelian gene, now there can seem little hope of finding a precisely identifiable gene producing a precise phenotypic trait ("the" gene for "yellow" peas). Perhaps the terminology for structural genes should be of gene subunits coded in DNA sequences and after the editing process of assembled genes, the latter transcribed into proteins. Some other terminology will serve for regulatory subunits and functional regulatory genes.

So many kinds of genes, however, make reference less and less specific. The once compact genetic locus has now been networked to and distributed across various loci entering in various ways to the phenotypic results. R. J. Britten and E. H. Davidson find a "web of possible interactions."[11] Evelyn Fox Keller concludes that the "complexity of regulatory dynamics puts the very concept of gene into jeopardy."[12]

Hans-Jorg Rheinberger concludes: "Today, it has become more reasonable, and it even might turn out to be sufficient, to speak of genomes, at least of 'genetic material' instead of genes, in the developmental as well as in the evolutionary dimension."[13] Philip Kitcher puts it similarly: "In molecular biological research, talk of *genes* frequently seems passé, a product merely of the accidents of history. There is no molecular biology of the gene. There is only molecular biology of the genetic material."[14]

We will have genomics, study of the networked system, but no genes in the genome, since every stretch of functional DNA is too "hooked up" to every other stretch to identify any stretch as a "gene for" this or that. Real genes are always in synthesis. Once we hoped to "carve nature at the joints," but the living organism is much more than jointed skeleton. One can carve up (dissect, segment) a living organism many ways, depending on the dimension of life studied, but the organism is an embodied multi-leveled whole: genotype to phenotype, morphology, metabolism, cells, organs, and behavior. Thomas Fogle predicts "the gene could become a quaint term of the past (at least in molecular biology circles) replaced by language that more accurately conveys relationships among domains contributing to phenotypic effects."[15]

But some will wonder whether domain-regions instead of gene-regions is not just substitute terminology. Geneticists have found that "development is surprisingly modular ... [and] this modularity ... implies that individual elements can be studied in isolation to provide meaningful answers."[16] "Modules" sounds like "joints." Proteins, such as enzymes, are often specific to their tasks. Population biologists suppose some kind of discrete units that assort in accord with the Hardy-Weinberg-Fisher rules. The creation of genetically modified (GM) organisms supports such modularity; the geneticists can transfer a stretch of DNA (a "gene," as they say) from the genome context in individuals in one species to the genome context of individuals in another species, and the GM species displays the transferred trait.

Complicated things are built with pieces and maintained by piecemeal replacements. Matt Ridley concludes that the webwork character still permits thinking of particulate inheritance: "Grey indeterminacy, variable causality and vague predisposition are the hallmarks of the system. This is not because...simple, particulate inheritance is wrong, but because simplicity piled upon simplicity creates complexity. The genome is as complicated and indeterminate as ordinary life, because it is ordinary life."[17] Something can be a mosaic and still be made of pieces.

Is gene proving to be not so much like "cell" as like "ecosystem"? There is a fact of the matter about cell boundaries; molecular biochemistry has not dissolved distinct cells. On the other end of the biological spectrum, however, is there a fact of the matter about ecosystems? Ecosystems cannot be delimited with clear boundaries, nor can characteristic processes (such as succession, equilibrium, etc.) always be reliably found there. Still, ecosystems have their niches, regions, and domains—fairly distinct parts that do interact in characteristic patterns. Investigators can focus on different ecosystem levels and dimensions and still think profitably about ecosystems. Similarly, researchers can keep the gene language around because it does make a helpful, if fuzzy, reference to different modular units on the genome that interact in maintaining the living organism and are transmitted in heredity. Indeed, it can be helpful to think of niches in ecosystems when we try to understand why this gene producing this behavior was selected whereas another producing a less well-adapted behavior was not.

Richard Burian concludes: "There is a fact of the matter about the structure of DNA, but there is no single fact of the matter about what the gene is. ...The concept of the gene is open rather than closed with respect both to its reference potential and its reference."[18] Kenneth Waters concludes: "In fact, molecular biologists seem to define gene in whatever way suits them at the time, and single texts typically present several conflicting definitions of the term. Some biologists seem to think that working with an ambiguous term is preferable to adopting a precise definition that will only need continual revision as knowledge advances."[19] Such an operational definition has been called a "consensus gene."[20] Geneticists in any context know more or less what they are talking about, and they communicate successfully with each other.

Despite these reservations of philosophers of biology, geneticists typically remain quite comfortable speaking of genes. In a textbook on genetics, Paul Berg and Maxine Singer define a molecular gene:

A eucaryotic gene is a combination of DNA segments that together constitute an expressible unit. Expression leads to the formation of one or more specific functional gene products that may be either RNA molecules or polypeptides. Each gene includes one or more DNA segments that regulate the transcription of the gene and thus its expression. Coding regions are DNA segments that encode a polypeptide or a functional RNA, or portions thereof. Those DNA segments whose sequences are not reflected in a gene product are called noncoding regions. Some noncoding regions, such as the regulatory signals that flank coding regions and the intervening sequence that interrupt coding regions, are parts of genes. Other noncoding regions, such as segments concerned with replication and segments of unknown significance, are found between genes and in special locations.[21]

High-volume nueleotide sequencing by machines has produced huge data arrays. The sequencers can decode the DNA stretches, but if geneticists are to interpret their results, they need some set of algorithms by which their machines can automatically locate what regions along the stretch are genes and what are not. This is done in genome science, bioinformatics, and (since this field so quickly enlisted computers for both storing and analyzing data) computational biology. The locating software often heavily depends finding sequences that are similar to those previously identified as genes in other genomes, or that can recognize open reading frames, transcription start and stop sites, and exon/intron boundaries. These computer programs are no better than the assumptions built into them—even if they can sometimes compute out of the massive data sets some results of our assumptions of which we were unaware.

One repeated discovery is that there has been conservation of many structural coding sequences, and especially of regulatory sequences, in animals with quite diverse morphologies. Geneticists speak of these as being the "same" genes; more technically they are homologous, similar because derived from a common ancestral gene and repeatedly used in many animal phyla. Such discoveries are evidence that some genetic units (genes, gene families, gene types, or whatever we call them) have been more or less stably maintained over millennia.

As noted earlier, genes that code for making cytochrome c molecules are extremely widely shared. The primary structure is identical in humans and chimpanzees, which diverged about 10 million years ago; there is only one replacement between humans and monkeys, whose most recent common ancestor lived 40 to 50 million years ago. Even between humans and yeast the code is more than half the same, and the differences are often inconsequential in function.[22]

Similar observations could be made regarding genes that code for proteins used in making adenosine triphosphate (ATP), biotin, riboflavin, hematin, thiamine, pyridoxine, vitamins K and B_{12}, or those involved in fatty acid oxidation, glycolysis, and the citric acid cycle. Such genes are used to produce products that are biologically rather like cultural artifacts such as nuts and bolts, light bulbs, zippers, resistors, capacitors, transistors. Once invented, molecules like acetylcholine, actin, myosin, and so on, are conserved, as are the genetic sequences used to produce them, and these show up as biological universals (more or less) in all kinds of organisms, from birds to rodents to humans. There are variations on such genes; evolutionary theory predicts both conservation and mutation. But the similarities are significant enough to call these conserved sequences homologous and orthologous genes.

THE CYBERNETIC GENE

The search for a molecular gene has been preoccupied with discovering *where* the gene is—where the DNA sequences are, where it stops and starts. But this could overlook intensive focus on *what* a gene is—its function, its distinctive character, or its role. The lingering question, staring us in the face all along, shifts the reference to the *information* located there. That is novel at the same time that it fuses the Mendelian units of inheritance with the molecular gene. When Paul Berg and Maxine Singer turn to define their molecular gene more briefly in an introductory work, the gene as a unit of information is central: "Gene: Initially, an abstract concept describing a unit of inherited information; now, a segment of DNA or RNA that constitutes a unit of inherited information."[23] This idea had been waiting in the wings; H. Kalmus suggested it decades before: "A gene, we may say, is a message, which can survive the death of the individual and can thus be received repeatedly by several organisms of different generations."[24]

The concept of "information" is so saturated through biochemistry and molecular biology texts that it is difficult to think how one could write such a text without talk of transcription, translation, signaling, message, copying, reading, coding, regulation, communication, or error. James D. Watson and Francis Crick had used the term "information" right at the start of their momentous study. "In a long molecule many different permutations are possible, and it

therefore seems likely that the precise sequence of the bases is the code which carries the genetic information."[25]

But both also expressed reductionist hopes, Crick wrote: "The ultimate aim of the modern movement in biology is in fact to explain *all* biology in terms of physics and chemistry. ...Eventually one may hope to have the whole of biology 'explained' in terms of the level below it, and so on right down to the atomic level."[26] Watson agreed: "Complete certainty now exists among essentially all biochemists that the other characteristics of living organisms...will all be completely understood in terms of the coordinative interactions of small and large molecules."[27] This put the focus on the molecular details of the coding. Subsequently, there has proved to be much more tension than they realized in reducing this information to nothing but physics and chemistry, with the claim that what is going on in DNA transcription is completely understood by discovering which molecule goes where with what bonding states. Analogously, in neurochemistry, tracing molecular movements in whatever fine detail imaginable, it would be difficult to comprehend what is taking place at a synapse without some concept of signals passing across the synapse.

Matter, energy, and genetic information

Life involves no new physical forces, no new chemical materials, but it does involve a new process and power, that of informational control of such forces and materials. A gene is a cybernetic unit, an information fragment. What is conserved is not the matter, not the organism, not the somatic self, not even the genes, but a message that can only be conserved if and only if it is distributed, disseminated. That may be the *sine qua non* of any complete account of what a gene is.

Several eminent, theoretically-oriented biologists, often working from an evolutionary perspective, have begun to insist on this cybernetic definition of a gene. George C. Williams is explicit:

> A gene is not a DNA molecule; it is the transcribable information coded by the molecule.[28]
>
> Evolutionary biologists have failed to realize that they work with two more or less incommensurable domains: that of information and that of matter....Matter and information [are] two separate domains of existence, which have to be discussed separately in their own terms. The gene is a package of information, not an object. ... Maintaining this distinction between the medium and the message is absolutely indispensable to clarity of thought about evolution.[29]

John Maynard Smith agrees: "Heredity is about the transmission, not of matter or energy, but of information. ...The concept of information is central both to genetics and evolution theory."[30] Biologists here can appeal to the founder of cybernetics. Norbert Wiener insists that 'Information is information, not matter or energy."[31]

In the physical and chemical sciences the fundamental properties of the universe lie in *matter* and *energy.* By Newtonian laws there is conservation of matter, also of energy; neither can be created or destroyed, although each can take diverse forms. Einstein integrated matter and energy, and conservation is reinterpreted from this framework, $E = mc^2$. Living things are constructed with the matter and energy familiar to physics; the novelty is that matter-energy now is found in diverse information states. Once, there were two metaphysical fundamentals. The physicists reduced these two to one: matter-energy; the biologists shortly afterward discovered that there were still two metaphysical fundamentals: *matter-energy* and *information.* In physics and chemistry as such, there can be only sources, never resources. In biology, the novel resourcefulness lies in the epistemic content conserved, developed, and thrown forward to make biological resources out of the physicochemical sources.

The chemists had found atoms, discrete units that can be variously assembled as molecules. The geneticists have found genes, discrete units that also can be variously assembled, also as molecules. However, there is a radical difference. When sodium and chlorine are brought together under suitable circumstances, anywhere in the universe, the result will be salt, sodium chloride. This capacity is inlaid into the atomic properties; the reaction occurs spontaneously. Energy inputs may be required for some of these inorganic results, but there is no information input needed. Neither the sodium nor the chlorine needs to be programmed to make salt, as though with a different program they might make something else.

When nitrogen, carbon, and hydrogen are brought together under suitable circumstances anywhere in the universe, with energy input, the spontaneous result may be ammo acids, but it is not hemoglobin molecules or lemurs. For that, there must be vital information, coded in DNA. All such information once upon a time did not exist, but came into place. Biologists do not know how this began, or at what stage the DNA coding appeared. But no one thinks that if you know quantum mechanics or the chemical table of elements you can predict the behavior of DNA molecules because DNA molecules are under

the sway of information—how to make a protein to make fur to survive winter—of which quantum mechanics and atomic chemistry know nothing.

The concept of regulatory genes intensifies this cybernetic dimension. Further, the dominant/recessive phenomenon and the distribution of alleles seem to have evolved as ways of carrying information potential that is infrequently expressed, recessive, maintained at low frequency in the heterozygous state until the environment changes and these genes-in-waiting become adaptive. None of this regulative or allelic activity makes any sense except cybernetically.

Genetic identity

Ask the question in terms of genetic identity. Where is a gene? The cybernetic answer differs from the molecular answer. Genome scientists, as we noted, report that they have identified the same gene in organisms from yeast to humans or that a gene has been conserved since Cambrian times. But if such similar DNA sequences have been repeatedly located, what constitutes their common identity? The "where" question transforms from one of physical location to informational location.

To make any sense of a gene surviving within and across species lines one needs cybernetic identity superimposed on a material identity that shifts over time. A gene is present in all cells where there are copies of it. Since genes are a kind of information, this is somewhat like asking where is the book, *War and Peace.* It is wherever there is a copy. So a particular gene is co-present in myriads of cells within any one individual, likewise co-present in relatives, copies within kin in a different skin, and, with many genes, co-present in quite distantly related lines. The last will have undergone some changes of sequences, some functional, some nonfunctional, but they will still be similar enough that geneticists refer to them as the same genes.

With the death of the organism, all its somatic genes start to rot. The chromosomes begin to decay or are digested by predators and scavengers and incorporated into something else. The molecules fall apart. Any particular gene-token is quite mortal All that can survive in any long term sense is the gene-type. A few genetic tokens are passed intergenerationally, one copy for each ancestor-descendant crossing. As the zygote develops, that one gene token thereafter

makes myriads of other gene tokens. If there is any genetic identity preserved, it is an identity of replicas.

The organismic self is a transient carrier of a ongoing historical line, receiving copies (in shuffled, mutated set) from predecessors, and, looking to the future, passing copies on (in shuffled, mutated set) to descendants. There is a short-range viewpoint from which an organism has its own genes; there is a long-range viewpoint from which any such "own genes" are "owned by" or "belong to" the genetic line that a particular self instantiates. Any particular organism has only some of the alleles, drawn from the populational pool, that are also being passed down the line.

The organism instantiates its genetic types; survival of the gene type is what counts. Its genes code the kind, representatively; and the organism, an expression of the kind, presents and re-presents the kind in the world. The genes have more of an eye on the species (so to speak) than on the individual. The solitary organism, living in the present, is born to lose; all that can be transmitted from past to future is its kind. Though selection operates on individuals, since it is always an individual that copes, selection is for the kind of coping that succeeds in copying, that is, re-producing the kind, distributing the information coded in the genes more widely. Fitness is not measured by an individual's own survival, long life, or welfare. Fitness is measured by what any individual can contribute to the next generation in its environment, fitness in the flow of life to pass life on. Survival of the fittest turns out to be survival of the better senders of whatever is of adaptive value in self into others in the next generation. That is cybernetic to the core.

Primary genetic information

Nevertheless, many philosophers of biology have reservations about the concept of information as applied to genes.[32] A common complaint is that the term is "only analogical." Molecules can't literally "know" any "code." What could "information" mean in a molecule? A deeper problem is that the term is difficult to make operational. Darwin famously introduced the metaphor of natural "selection" and made it powerfully descriptive of what is going on in evolutionary history. Selection is first something we experience in ordinary life, including the activity of breeders, and by extended meaning evolutionary processes "select" the fittest. Biologists can filter out the intentional element; the remainder does describe differential survival

processes. Population geneticists have found ways to operationalize, to quantify selective pressures. Can geneticists do the same thing for 'Information," "coding," "reading"?

Humans first know the meaning of the word "information" in our own experience. To speak of information in DNA is, at least initially, metaphorical. Are we to say the same of terms such as "translation"? The term "translate" usually means to move from one language system to another; the DNA is a symbol system, but the resulting protein molecule is not another symbol system, so perhaps "transcription" is a less metaphorical term? "Synonym" is a term first learned in human language, then applied to differing codons that result in the same amino acid. It will be difficult to strip out all the terms that start as metaphors from ordinary life: "adapt," "function," "correct," "mistake," "genetic memory," "start," "stop," "develop," "regulate," "change," "evolve."

We first experience chains in ordinary life, made of iron links. The word "chain" is applied to polypeptide linkages, metaphorically. But it does not follow that a polypeptide chain is not a descriptive term. Chain has become a familiar term for any serial linkage—a chain of command—and is here serving to portray the serial linkage of amino acids. Genes make "copies" of these chains. That word too, one can insist, is metaphorical, but it does not follow that "copy" is not an authentically descriptive term. Various words, such as "replicate," "regenerate," "reproduce," "activate," "inhibit, "start," "stop," "cut," "splice," "error," "correct," enable scientists to recognize qualitative, substantive similarities, with insight into how processes work, using comparisons between familiar and unfamiliar systems. So also with "information." Strip all this dimension out, and you will not understand what is going on.

The idea of 'coding' drove the Watson-Crick research program. If they had been looking for chemistry and nothing but chemistry—how this atom bonds to that atom—they would not have made these discoveries. They had to be looking for a code. Chemically, in forming the chains, one atom bonds to another atom in the same way no matter whether the chain produced is functional or if the bonding is made during some mismatch in which the reading frame shifts and an abortive chain is formed. The three groups of bases "symbolize" an amino acid; the long DNA molecule with its sequenced groups of three "symbolizes" protein units—even if some pieces have to be cut out (introns) and the others (exons) re-assembled as the final protein is made.

The laws of physics and chemistry, used in the coding, do not change over the millennia of evolution. But changes in the sequences of the DNA and resulting protein molecules introduce radical changes in the forms of life on Earth. There are no new laws of chemistry and physics, though there might be some laws of chemistry and physics that earlier were nowhere exemplified that are exemplified later in novel biochemistry. Yet new functions are regularly coded into the DNA and expressed in the proteins they produce and behaviors they support—how to live on land or how to nurse a baby.

The term "information" is complex and has been used variously in differing sciences. There is information on the surface of the moon, in the sense that a geologist can read some of the history of the moon from the overlay of meteoric impacts there. There is information in DNA such that a biologist interested in phylogenetic history can use cladistics (the method of taxonomic classification analyzing shared properties to group organisms), in order to read how closely the mammals are related to the reptiles by analysis of similarities in DNA. But the craters on the moon are not themselves doing any reading, nor is the DNA itself reading its ancient evolutionary history.

Mathematical information (or communication) theory deals with reliable signal transmission, without regard to the significance of the signal transmitted—whether Shakespeare or gibberish. The term "information" is almost misapplied here, since it has nothing to do with the semantic value, importance, meaning, or function of the signal sequence transmitted. According to Shannon-Weaver's "transmission" model of communication, there would be just as much information transmitted in any nonsense DNA (so-called) as in the genetically significant DNA. If the sequence, even a senseless signal gets through, and the system reliably reproduces nonsense, then there has been information transfer. By contrast, relevant information has both signal reliability and signal significance.

Making some sense of biological information is reasonably straightforward at the first, code-script level; the codons encrypting a polypeptide sequence. Initially both significant and insignificant sequences are reliably transmitted and transcribed; later, cutting out introns and splicing exons, under genetic regulatory sequences, a reliable and biologically significant signal gets through. This is something like reading a newspaper and attending to some relevant stories and skipping others. Or, changing the metaphor, it is like using an old computer with a fragmented main hard drive, where

important information is mixed at times with no longer used programs, leftover text bits and pieces, and isolated viral programs. It is something like living in an old house, which one can do well, even efficiently, although there is lots of infrequently used stuff lying about, some of it kept around because it might become important again.

Messages need both integration and segmentation. Human speech requires words, with spaces, and arranged into sentences, with starts, stops, punctuation. Sentences go into paragraphs; a coherent text is a webwork of linguistic parts. Genetic material will not have directly analogous grammar: nouns, verbs, or adjectives. Speakers of a language will be self-consciously aware of what they intend to say; there is no genetic analogue. But if messages are conveyed about the structure and metabolism of functioning organisms with diverse parts integrated into a whole, there will be both integration and components. Some components will specify structure (like nouns, as it were). Others will promote and regulate active process (like verbs). Others will modify process and structure (like adverbs and adjectives). Language is a functional webwork of semantic units; analogously a genetic "text" is a functional webwork of biologically significant units.

The transcription process is linear, one-dimensional, one-directional, with a spot focus moving along codon by codon (word by word) picking up the sequence needed to construct the protein or regulatory product. This makes "reading" a helpful analogy, although again there is no self-conscious "reader." The reading is multi-leveled; the DNA is scanned, 3-letter frame by frame. There is cutting and splicing of the primary reading, exons retained and introns excised, to assemble a sequence amino acid by ammo acid, end on end. Such reworking of the transcription output is regularly termed "editing," another metaphorical and cybernetic word. Molecules cannot edit. Enzymes can cut and splice, and if they do so "in order to" filter out the unneeded parts of the transcription and get the right sequence for maintaining metabolism, it does seem to require some kind of discriminating "know how." This is yet another level of selecting "for" components that the organismic metabolism requires. At the phenotypic level, the organism, a somatic self, is using such transcription and editing to read out vital information in the defense of its life. In reproduction such information is being transmitted ("read") from one generation to the next in order to maintain the species line.

Computing analogies are also apt. "The machine code of the genes is uncannily computerlike. Apart from the differences in jargon, the pages of a molecular-biology journal might be interchanged with those of a computer-engineering journal."[33] Computers also employ such serial reading: a message is coded into bits and bytes, translated from one form to another, and the process is subject to precise analysis, simultaneously mechanistic and informational. The computer analogy is quite limited, however, as we notice below, because computers are neither alive nor subject to natural selection.

In transcription, there is information flow in one direction from DNA to phenotype. There is no analog in chemistry or physics to this "central dogma" of molecular biology. Information in another sense flows the other way, phenotype to DNA, when organismic demands determine what sequences of the DNA are used, switching it on and off, editing the transcription, and regulating its use. DNA makes proteins, via the complex processes earlier recognized. In due course these proteins, organized in the cell, make more DNA. But where the germ line is separated from the somatic cells, these proteins do not determine the information sequence in the reproductive DNA they make. Nor in somatic metabolism does protein "know how" to make more protein directly; there is no such information flow. That information is segmentally coded in the linear DNA sequence and is read out and selectively used from there. Without this sequence information, no functioning proteins can be made.

When biologists speak of natural selection, they can, as I stated above, filter out the intentional element. But can geneticists similarly filter out the intentional element? Yes, of course, is a first reply; genes cannot intend anything any more than can the forces of natural selection operating on genes. But thinking further, the process of genes unzipping and transcribing their sequences is, so to speak, "headed" somewhere. The sequence specifies an ordered trajectory that leads to highly complex organized functional systems. A genetic sequence has a potential for being an ancestor in an indefinitely long line of descendant genotype/phenotype re-incarnations.

The gene does not contain simply descriptive information "about" but prescriptive information "for." The gene will be a gene "for" a trait because there has been natural selection "for" what it does contributing to adaptive fit.[34] The preposition "for" saturates both natural selection and genetics. Traits get "selected for"; and the pattern, the code "for" this gets simultaneously "selected for" in the genes, "mapped" there, the genotype that records the know-how to

make the material and processes in the phenotype. The intentional aspect of "for" in natural selection can be eliminated; the mutation and shuffling process is blind, random. Some recent geneticists think the process more probabilistic; there may at times be selection "for" more capacity to mutate in some regions of the genome than others, or for certain kinds of mutations. Mutations rates may be increased in times of stress.

Geneticists are now speaking of "natural genetic engineering" of DNA changes as the "21st century view of evolution."[35] John H. Campbell writes, "Cells are richly provided with special enzymes to tamper with DNA structure," enzymes that biologists are extracting and using for genetic engineering. But this is already going on in spontaneous nature: "Gene-processing enzymes also engineer comparable changes in genes in vivo. Cells deliberately manipulate the structures of their gene molecules for phenotypic and possibly evolutionary goals.... We have discovered enzymes and enzyme pathways for almost every conceivable change in the structure of genes. The scope for self-engineering of multigene families seems to be limited only by the ingenuity of control systems for regulating these pathways."[36] His use of "deliberately," like the parallel use of "intentional" cannot involve conscious deliberation, but rather refers rather to a problem-solving search (Latin: *deliberatio,* well weighed), that is, to trials systematically ventured and tested. In the immune system, for instance, forming B cells, the organism rearranges various DNA segments to produce a high number of differently specific immunoglobulin molecules out of a relatively small number of gene segments. Meanwhile, all these genetic and cellular activities are "for" something vital.

In the results that the non-intentional natural selection process produces, the genes do act directed toward a future, under construction. Unlike natural selection, wherever it shows up in genetics, there is a "telos" lurking in that "for." Ernst Mayr coined the term "teleonomic" for biological functions, contrasted with simple causation in physics and chemistry, also contrasted with "teleological," which, he thought, had objectionable overtones of conscious intent. What genes have is a "telos," an "end." Magmas crystallizing into rocks, and rivers flowing downhill have results but no such "end." Organisms are biological agents; the phenotypes are doing something, maintaining their form of life; and they succeed because within them are genes which are also biological agents, doing something, maintaining this form of life. Genes are proactive.

Rather than wishing to filter out the intentional elements in biology, some theoretical biologists and philosophers have, interestingly, begun using the term "intentional" as descriptive of biological information in genes. John Maynard Smith insists: "In biology, the use of informational terms implies intentionality."[37] That word, again, may have too much of a "deliberative" component for most users, but what is intended by "intentional" is this directed process, going back to the Latin: *intendo,* with the sense of "stretch toward," or "aim at." If you are uncomfortable with "intends," the DNA "attends" to a project. Genes have both descriptive and prescriptive "aboutness"; they do stretch toward what they are about. This forward component what is caught by the term "intentional," even when the conscious intention is not present. The DNA molecule is disposed, tensed, toward a future, a "will be," even with a "will" to it. It is set to "go. " This is tropistic behavior.

Kim Sterelny and Paul E. Griffiths speak of "intentional information" in contrast to "causal information": "Intentional information seems like a better candidate for the sense in which genes carry developmental information and nothing else does."[38] Intentional or semantic information is for the purpose of ("about") producing a functional unit that does not yet exist. It is *teleosemantic.* Where there is information being transmitted, there arises the possibility of mistakes, of error. The DNA, which "intends" to make a certain amino acid sequence that will later fold into a protein segment, can be misread. If the reading frame gets shifted off the correct triplet sequence, then the wrong amino acids get specified and the assemblage fails. There is mismatch. Often there is machinery for "error-correction." None of these ideas make any sense in chemistry or physics, geology or meteorology. Atoms, crystals, rocks, and weather fronts do not "intend" anything and therefore cannot "err."

A mere cause is pushy but not forward looking. A developing crystal has the form, shape, location it has because of, on the cause of, preceding factors. A genetic code is a "code for" something. The code is set for control of the upcoming molecules that it will participate in forming. If we use the word "control" with crystal formation (the size of the crystals is controlled by the temperature at formation), this control refers to the past. By contrast, genetic control faces forward. There is proactive "intention" about the future.

Organismic information

At higher levels the sense of information is more elusive. Do the genes code a program for the whole organism? Are they webworked so that the development of the embryo and the maintenance of the adult is all front-loaded into the genome, unfolding as an acorn seems to unfold into an oak? Does the oak bubble up out of the genome? Morphology and metabolism are four-dimensional events in space and time; the DNA code-script is spiral linear sequence, both the structural and the regulatory portions. The secondary and tertiary folding comes more or less spontaneously once the primary amino acid sequence of the protein is specified, although at times the organism uses "chaperones" to fold the primary sequence this way and not that.

One can have the score of a symphony and lack the capacity to play it; something must orchestrate the score. Is there a conductor orchestrating the players? The process is not like playing a video on a VCR, the machine decodes and spits out what's on the tape. Erwin Schrödinger said, famously, that genes are "law-code and executive power — or ... architect's plan and builder's craft."[39] But this seems not to be the case. The organism selects what to play, and improvises on the themes, cutting and splicing here and there, depending on the circumstances and needs of the organism. The initial transcription (the "read out") is rather stereotyped, but soon the organism becomes more like an interactive "reader." The genome is more like a recipe that the organism cooks, though in the zygote it seems something like a self-cooking recipe, given a resourceful pot.

In the adult organism, the organism as a whole is in control of the DNA as a resource kit. But in transmission to the next generation, there is a point at which the organism has to go through a bottleneck stripped down to concentrated information, the sperm and egg forming a zygote. True, the mother has the zygote embedded in her womb, without which it will instantly perish. But the coding instructions in the zygote are unfolding from the DNA contained there; in the first cells of embryogenesis there is as yet no organism to control it. Computer metaphors break down with this one-cell, one-DNA-set transition unfolding into the complex whole organism. No computers reproduce themselves by passing a single set of minute coding sequences from one generation of computers to the next, with the next generation of computers self-organizing from this single transferred information set.

A single totipotent cell, using maternal resources provided, transforms itself into a total complex organism. The instructions and impetus for this transformation all seem loaded into the DNA. If not there, then where else? But exactly where is this overall program? That is not so easy to say. There seems no executive master gene (analogous to a brain in an animal body). With some regulatory genes, there is a hierarchy of control. But often there seems more a parliament of genes, cross-talking to each other, activation and inhibition, enzymatic interplay, feed-forward loops, feedback loops, control and counter-control, cascading, and so on.

Although at the primary level, with code-script transcribed, the concept of gene as information fragment is required and more or less manageable, at the whole organism level geneticists do not have any larger-scale units of information. It is difficult to quantify organ-level morphology or metabolism. Geneticists can say whether more genetic sequence is required to build a liver than a kidney, but if they were to say (as many might) that the liver processes more information than the kidney, or try to quantify the information flows between liver and kidney, they would be at a loss for units. The cybernetic gene is now to be measured not by the number of codons, but by its performative capacity. The DNA has serialized a vital organic morphology and metabolic process; the four-dimensional, multi-leveled organism, biomolecules to ecosystem, is where such information is functionally enacted. Genes may contain information that motivates birds to build nests, or to migrate in autumn, but there are no operational units for the analysis of information at such levels. Genes carry the information that elk should flee the approaching hunter or that the plant with disturbed roots should secrete repair products and rebuild roots prospective to survival through winter, but geneticists can produce no taxonomy of such information. At present it is impossible to model information at this level in effective, operational form. One of the promises of systems theory is that one day we may be able to do so. "The apparently magical nature of intentional information is one of the major objections to a materialistic account of thought," note Sterelny and Griffiths.[40] Perhaps the conclusion to draw is that genes have a cybernetic dimension that is immaterial, superposed on the material.

Searching genes

A gene is an information fragment in an organismic/genomic/species search program. This both complements and contrasts with their

conservation function. Genes are as dynamic as they are stable units. Mutation, crossing-over, drift, allelic variation, cutting and splicing, insertions, deletions—all this disrupts conserving the same genes; but such processes make genes what they are: information generators. Genes generate trial and error solutions, some of which will yield novel information discovered. Interweaving possibilities and producing new possibility space by shuffling around bits and pieces is the business of genes. This is what Campbell was calling "genetic engineering." As a result of this evolutionary exploring over time, there is, as Francisco Ayala puts it, "increase in the ability to gather and process information about the environment."[41]

"Search" is another bothersome metaphorical word. Humans deliberately search; when applied to genes can (or ought) we to filter out the intentional element? We might say that plant roots (nondeliberately) "seek" for water, or that the immune system generates variant antibodies in a cybernetic process selected to "find" one that "defends" against invading pathogens. None of this is self-consciously "intentional," but, recalling the "stretching toward" or "aiming at," it seems again that genes as much as roots or immunoglobulins are also (nonintentionally) naturally selected to function in this exploratory way. Genes are set to generate biodiversity without end.

Cybernetic genes are open, as much as are they deterministic. Natural history is the story of transformations as much as of evolutionary stability. This is *in*formation more or less in *trans*formation. Maynard Smith points this out, in another analogy to language: "There are today, in the living world, only two systems capable of... transmitting an indefinitely large number of different messages: these are the genetic system... and human language."[42] Genes speciate new kinds in response to environmental challenge, as much as reproduce existing kinds to the maximum extent possible. There is descent with modification, and this sometimes results in ascent with modification. Survival of the fittest is a subroutine in a bigger story: survival of the searchers.

In one species the searching genes outdo themselves. Elaborating the genetic cybernetic possibilities, in generating humans genes crossed a threshold into a cognitive realm with spectacular new powers and freedoms. Geneticists have recently also sequenced the chimpanzee genome, and after comparing it with the human genome, they are still trying to figure out how so few genetic differences made such a dramatic critical change.[43] Richard Lewontin puts it this way:

> Our DNA is a powerful influence on our anatomies and physiologies. In particular, it makes possible the complex brain that characterizes human beings. But having made that brain possible, the genes have made possible human nature, a social nature whose limitations and possible shapes we do not know except insofar as we know what human consciousness has already made possible....The genes, in making possible the development of human consciousness, have surrendered their power both to determine the individual and its environment. They have been replaced by an entirely new level of causation, that of social interaction with its own laws and its own nature.[44]

J. Craig Venter and his 200 geneticist co-authors call this crossing "a massive singularity that by even the simplest of criteria made humans more complex" than anything preceding in genetics; hence their warning, with which we began, against determinism and reductionism.[45] Such determinism and reductionism, it turns out, is neither human nature nor genetic nature.

This genetically-launched searching continues in our search to understand genes. Curiously, a (nonintentional) natural selection process results in intentional genes. These (nondeliberative) intentional genes, in their searching, result in humans with their deliberative intentions and massive cognitive powers, of which these geneticists deliberatively decoding their own genome and re-searching whether and how to reform their genes is a striking example. A philosopher wondering about this is using his genetically-organized molecules to do metaphysics. Despite those misgivings of philosophers of science, there does almost seem to be some "magical nature"[46] here. Little wonder we are still challenged when trying to fit genes into our comprehensive worldview.

NOTES

[1] Petter Portin, "The Concept of the Gene: Short History and Present Status," *Quarterly Review of Biology* 68, no. 2 (1993): 207.

[2] Quoted in Leon Jaroff, "The Gene Hunt," *Time* 133, no. 12 (20 March, 1989):67.

[3] J. Craig Venter, et al. "The Sequence of the Human Genome," *Science* 291(2001):1348.

[4] Chris Gunter and Ritu Dhand, "The Chimpanzee Genome," *Nature* 437(1 September 2005):47.

[5] R. E. Dickerson, "The Structure of Cytochrorne c and the Rates of Molecular Evolution," *Journal of Molecular Evolution* 1(1971): 26-45.

[6] Wilhelm Johannsen, *Elemente der exakten Erblichkeitslehre*, Jena: Gustav Fischer, 1909.

[7] T. H. Morgan, A. H. Sturtevant, H. J. Muller, and C. B. Bridges, *The Mechanism of Mendelian Heredity*, New York: Henry Holt, 1915.

[8] Human Genome Project, *Primer on Molecular Genetics*, 1998. http://www.ornl.gov/hgmis. Accessed on November 19, 2005.
[9] David L. Stern, "Evolutionary Developmental Biology and the Problem of Variation," *Evolution* 54 (2000): 1079-1091, and references therein.
[10] F. Jacob and J. Monod, "Genetic Regulatory Mechanisms in the Synthesis of Proteins," *Journal of Molecular Biology* 3 (1961):334.
[11] R. J. Britten and E. H. Davidson, "Gene Regulation for Higher Cells: A Theory," *Science* 165(1969):349-357.
[12] Evelyn Fox Keller, *The Century of the Gene* (Cambridge: Harvard University Press, 2000), p. 69.
[13] Hans-Jörg Rheinberger, "Gene Concepts: Fragments from the Perspective of Molecular Biology," in *The Concept of the Gene in Development and Evolution*, eds. Peter J. Beurton, Raphael Falk, and Hans-Jörg Rheinberger (Cambridge: Cambridge University Press, 2000), p. 232.
[14] Philip Kitcher, "Genes," *British Journal for the Philosophy of Science* 33(1982):357.
[15] Thomas Fogle, "The Dissolution of Protein Coding Genes in Molecular Biology?" in *Concept of the Gene*, eds. Beurton et al. (Cambridge: Cambridge University Press, 2000) p. 23.
[16] Stern, "Evolutionary Developmental Biology and the Problem of Variation," pp. 1087-1088.
[17] Ridley, Matt, *Genome: The Autobiography of a Species in 23 Chapters* (New York: Harper Collins, 2000), p. 75.
[18] Richard M. Burian, "On Conceptual Change in Biology: The Case of the Gene," in *Evolution at a Crossroads: The New Biology and the New Philosophy of Science*, eds. D. J. Depew and B. H. Weber (Cambridge: The MIT Press, 1985), p. 37.
[19] C. Kenneth Waters, "Genes Made Molecular," *Philosophy of Science* 61 (no. 2, 1994): 178.
[20] Fogle, "Dissolution of Protein Coding Genes in Molecular Biology," pp. 3-6.
[21] Maxine Singer and Paul Berg, *Genes and Genomes: A Changing Perspective* (Mill Valley: University Science Books, 1991), pp. 622-623.
[22] Dickerson,"The Structure of Cytochrome c and the Rates of Molecular Evolution"; Walter M. Fitch and Emanuel Margoliash, "Construction of Phylogenetic Trees," *Science* 155 (1967): 279-284.
[23] Paul Berg and Maxine Singer, *Dealing with Genes: The Language of Heredity* (Mill Valley: University Science Books, 1992), p. 247.
[24] H. Kalmus, "A Cybernetical Aspect of Genetics," *Journal of Heredity* 41, no. 1 (1950):19.
[25] James D. Watson and Frances Crick, "Genetical Implications of the Structure of Deoxyribonucleic Acid," *Nature* 171(1953): 967.
[26] Francis Crick, *Of Molecules and Men* (Seattle: University of Washington Press, 1966), p. 10, p. 14.
[27] James D. Watson, *Molecular Biology of the Gene*, 3rd Ed. (Menlo Park, CA: W.A. Benjamin, 1976) p. 54.
[28] George C. Williams, *Natural Selection: Domains, Levels, and Challenges* (New York: Oxford University Press, 1992), p. 11.
[29] Quoted in John Brockman, *The Third Culture: Beyond the Scientific Revolution* (New York: Simon and Schuster, 1995), p. 43.

[30] John Maynard Smith, "Life at the Edge of Chaos?" *New York Review of Books* 52, no. 4 (March 2, 1995):28.
[31] Norbert Wiener, *Cybernetics* (New York: John Wiley, 1948), p. 155.
[32] Kim Sterelny and Paul E. Griffiths, *Sex and Death: An Introduction to Philosophy of Biology* (Chicago: University of Chicago Press, 1999), p. 105.
[33] Richard Dawkins, *River out of Eden* (New York: Basic Books, 1995), p. 17.
[34] We might speak of a "gene for" red eyes, even if we knew no differential survival advantage. Oncogenes are likely to cause cancer, but these are aberrant or mis-regulated genes.
[35] James A. Shapiro, "A 21st Century View of Evolution: Genome System Architecture, Repetitive DNA, and Natural Genetic Engineering," *Gene* 345(2005): 91-100.
[36] John H. Campbell, "Evolving Concepts of Multigene Families," In *Isozymes: Current Topics in Biological and Medical Research*, Volume 10: *Genetics and Evolution* (!983):408-409.
[37] John Maynard Smith, "The Concept of Information in Biology," *Philosophy of Science* 67(2000): 177.
[38] Sterelny and Griffiths, *Sex and Death*, p. 104.
[39] Erwin Schrodinger, *What Is Life?* (Cambridge: Cambridge University Press, [1944] 1951), p. 21.
[40] Sterelny and Griffiths, *Sex and Death*, p. 105.
[41] Francisco J. Ayala, "The Concept of Biological Progress," in *Studies in the Philosophy of Biology*, eds. Francisco Jose Ayala and Theodosius Dobzhansky (New York: Macmillan, 1974), p. 344.
[42] John Maynard Smith, "Reply to Commentaries," *Philosophy of Science* 67 (2000):215.
[43] Chimpanzee Sequencing and Analysis Consortium, "Initial Sequence of the Chimpanzee Genome and Comparison with the Human Genome," *Nature* 437 (2005):69-87.
[44] R. C. Lewontin, *Biology as Ideology: The Doctrine of DNA* (New York: Harper Collins Publishers, 1991), p. 123.
[45] Venter, et al, "Sequence of the Human Genome," pp. 1347-1348.
[46] Sternely and Griffiths, *Sex and Death*, p. 105.

REFERENCES

Ayala, Francisco, J. "The Concept of Biological Progress." In *Studies in the Philosophy of Biology*. Edited by Francisco Jose Ayala, Theodosius Dobzhansky, 339-355. New York: Macmillan, 1974.

Berg, Paul and Maxine Singer, *Dealing with Genes; The Language of Heredity*, Mill Valley, CA: University Science Books, 1992.

Britten, R. J. and E. H. Davidson. "Gene Regulation for Higher Cells: A Theory." *Science* 165 (1969): 349-357.

Brockman, John. *The Third Culture: Beyond the Scientific Revolution.* New York: Simon and Schuster, 1995.

Burian, Richard, M. "On Conceptual Change in Biology: The Case of the Gene." In *Evolution at a Crossroads: The New Biology and the New Philosophy of Science.* Edited by D. J. Depew, B. H. Weber, 21-42. Cambridge: The MIT Press, 1985.

Campbell, John H. "Evolving Concepts of Multigene Families," In *Isozymes: Current Topics in Biological and Medical Research,* Volume 10: *Genetics and Evolution* (1983):401-417.

Chimpanzee Sequencing and Analysis Consortium, "Initial Sequence of the Chimpanzee Genome and Comparison with the Human Genome," *Nature* 437 (2005): 69-87.

Crick, Francis. *Of Molecules and Men.* Seattle: University of Washington Press, 1966.

Dawkins, Richard. *River Out of Eden.* New York: Basic Books, 1995.

Dickerson, R. E. "The Structure of Cytochrome c and the Rates of Molecular Evolution." *Journal of Molecular Evolution* 1 (1971): 26-45.

Fitch, Walter, M., and Emanuel Margoliash. "Construction of Phylogenetic Trees." *Science 155* (1967): 279-284.

Fogle, Thomas. "The Dissolution of Protein Coding Genes in Molecular Biology." In *The Concept of the Gene in Development and Evolution.* Edited by Peter J. Beurton, Raphael Falk, and Hans-Jörg Rheinberger, 3-25. Cambridge: Cambridge University Press, 2000.

Gunter, Chris and Ritu Dhand. "The Chimpanzee Genome." *Nature* 437 (1 September, 2005): 47.

Human Genome Project Information. *Primer on Molecular Genetics.* 1998 http://www.ornl.gov/hgmi. Accessed on November 19, 2005.

Jacob, F. and J. Monod, "Genetic Regulatory Mechanisms in the Synthesis of Proteins." *Journal of Molecular Biology 3* (1961): 318-356.

Jaroff, Leon. "The Gene Hunt." *Time* 133, no. 12. (20 March, 1989): 62-67.

Johannsen, Wilhelm. *Elemente der exakten Erblichkeitslehre.* Jena: Gustav Fischer, 1909.

Kalmus, H. "A Cybernetical Aspect of Genetics." *Journal of Heredity* 41, no. 1. (1950): 19-22.

Keller, Evelyn Fox. *The Century of the Gene.* Cambridge: Harvard University Press, 2000.

Kitcher, Philip, "Genes." *British Journal for the Philosophy of Science* 33 (1982): 337-359.

Lewontin, R.C. *Biology as Ideology: The Doctrine of DNA.* New York: HarperCollins Publishers, 1991.

Maynard Smith, John, "Life at the Edge of Chaos?," *New York Review of Books* 52, 4. (March 2, 1995): 28-30.

Maynard Smith, John. "The Concept of Information in Biology." *Philosophy of Science* 67 (2000): 177-194.

Maynard Smith, John. "Reply to Commentaries." *Philosophy of Science* 67 (2000): 214-218.

Morgan, T. H., A. H. Sturtevant, H. J. Muller, and C. B. Bridges, *The Mechanism of Mendelian Heredity.* New York: Henry Holt, 1915.

Portin, Peter, "The Concept of the Gene: Short History and Present Status." *Quarterly Review of Biology* 68, no. 2. (1993): 173-223.

Rheinberger, Hans-Jörg. "Gene Concepts: Fragments from the Perspective of Molecular Biology." In *The Concept of the Gene in Development and Evolution.* Edited by Peter J. Beurton, Raphael Falk, and Hans-Jörg Rheinberger, 219-239. Cambridge: Cambridge University Press, 2000.

Ridley, Matt *Genome: The Autobiography of a Species in 23 Chapters.* New York: Harper Collins, 2000.

Schrödinger, Erwin, *What Is Life?* Cambridge: Cambridge University Press, [1944] 1951.

Shapiro, James A. "A 21st Century View of Evolution: Genome System Architecture, Repetitive DNA, and Natural Genetic Engineering." *Gene* 345 (2005): 91-100.

Singer, Maxine and Paul Berg. *Genes and Genomes: A Changing Perspective.* Mill Valley, CA: University Science Books, 1991.

Stern, David L. "Evolutionary Developmental Biology and the Problem of Variation." *Evolution* 54 (2000): 1079-1091.

Sterelny, Kim, and Paul E. Griffiths. *Sex and Death: An Introduction to Philosophy of Biology.* Chicago: University of Chicago Press, 1999.

Venter, J. Craig et al. 'The Sequence of the Human Genome." *Science* 291 (2001):1304-1351.

Waters, C. Kenneth, "Genes Made Molecular." *Philosophy of Science* 61, 2. (1994): 163-185.

Watson, James D. *Molecular Biology of the Gene* 3rd ed. Menlo Park, CA: W. A. Benjamin, 1976.

Watson, James D. and Frances Crick. "Genetical Implications of the Structure of Deoxyribonucleic Acid." *Nature* 171 (1953): 964-967.

Wiener, Norbert. *Cybernetics.* New York: John Wiley, 1948.

Williams, George C. *Natural Selection: Domains, Levels, and Challenges,* New York: Oxford University Press, 1992.

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