# Unraveling the secret of life
# DNA Self-duplication, the Basic Precept of Biotechnology, Is Denied

*Barry Commoner*

The title of James Watson's new book, *DNA: The Secret of Life*, echoes the boast voiced on the day, fifty years ago, when he and Francis Crick discovered the structure of this now-famous molecule[1]. The inexplicable uniqueness of life has for centuries been mystery enough to elicit religious doctrine, let alone scientific research. Therefore it is fitting that, to celebrate the fiftieth anniversary of the double helix, *Time's* February 17, 2003 cover depicts an updated Adam and Eve standing before the biblical tree of life, each entwined in the coils of a golden helix anatomically placed to symbolize their recent loss of innocence[2]. In the story itself, "Solving the Mysteries of DNA", *Time* tells us the long-sought secret that Watson and Crick's scientific discovery revealed: "The beauty of DNA is that its form is its function. It's a self-reproducing molecule that carries the instructions for making living things from one generation to the next." An accompanying molecular diagram explains exactly "How DNA Works" by making "a copy of itself."

*Time's* story line accurately reflects Watson and Crick's original account. Although, of all known forms of matter, only a living thing is endowed with the prodigious power of self-replication, that power, they believed, originates exclusively in one of its lifeless chemical components -DNA. This idea is embodied in the most frequently quoted sentence in their celebrated one-page letter to *Nature*, published on April 25, 1953: "It has not escaped our attention that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."[3] The sentence refers to a crucial feature of the DNA double helix: the two DNA strands are so aligned that their four types of constituent nucleotides (A, T, C and G) form complementary pairs. In the double helix, in which each strand may be comprised of a linear array of thousands of nucleotides, the nucleotide A in one strand is always positioned across from nucleotide T in the other strand, and similarly, G is located opposite C. These pairings are enforced by a particular intermolecular link -the hydrogen bond - between each of the paired nucleotides.

On May 30, 1953, this time in a two-page paper, also published in *Nature*, Watson and Crick defined "...the essential operation of a genetic material [as] that of exact self-duplication."[4] That the paired nucleotides are held together by hydrogen bonds in the double helix suggested to them a plausible mechanism for the exact self-duplication of DNA: A single parental DNA strand's nucleotide sequence is replicated simply by attracting to itself, by means of hydrogen bonds, the complementary nucleotides that are freely available in the cell. These are thereby aligned and incorporated into a new DNA strand, to form a complementary version of the parent strand's nucleotide sequence. Later, in 1958, Crick explained that the DNA's nucleotide sequence is the genetic information which, transferred to the cell's proteins, determines their chemical specificity and therefore the inherited traits they engender[5].

Watson and Crick were aware, however, that once a newly acquired free nucleotide is properly lined up on the parental DNA template, the chemical bond that links it to the next nucleotide in the growing strand must be formed -a biochemical task, polymerization, requiring an enzyme. In 1956, Arthur Kornberg discovered such an enzyme, DNA polymerase, in a wide array of organisms[6]. His test-tube experiments showed that in a mixture containing a pre-existing DNA template, a supply of the four types of nucleotides, and DNA polymerase (a protein purified from tissue or bacteria), a new strand of DNA is formed, joined to the template by the hydrogen-bonded complementary nucleotide pairs. Kornberg concluded that in such experiments, "The unifying base generalization about the action of this enzyme [DNA polymerase] is that it catalyzes the synthesis of a new DNA chain in response to directions from a DNA template; these directions are dictated by the hydrogen-bonding relationship of adenine [A] to thymine [T] and of guanine [G] to cytosine [C]."[7]

By the 1960s a new and rapidly growing breed of researchers, molecular biologists, were convinced by the Watson-Crick theories and Kornberg's experiments. Impelled by the idea that Watson told the *Time* writer was "too good not to be true," they turned DNA into an experimental powerhouse. If the DNA of the gene for human erythropoietin, essential for red blood cell production, contains all the genetic information needed for its own replication, why not insert the gene into hamster cells, enabling them to produce this valuable protein and replacing the repeated transfusions needed by anemia patients [8].On the same grounds, why not inject the gene itself into patients, who could then continue to produce the protein on their own? Also, if DNA is universally able to govern the course of inheritance, including development, why not clone rather than breed the most productive domestic animals? Lurking only slightly off-stage is the proposal, advanced by even a few Nobel notables, to insert into human embryos replacements for genes which are linked to inherited disease - or, as Watson has suggested, stupidity and ugliness[9].

All of these biological ventures were conceived in the belief that the gene contains the only information needed to specify an inherited trait and that, by replicating itself, it ensures its own propagation and the trait's as well. This theoretical autonomy of the gene - that it can maintain and propagate its distinctive specificity in *any* biological context - is a consequence of that wholly unprecedented belief that a lifeless chemical has, within itself, the power of self-duplication. The huge and still growing edifice of molecular biomedical and agricultural research and technology rests on the validity of that concept.

However, the outcome of experimental biological transformations, grounded in the conventional interpretation of gene replication, suggests that these applications have been troubled by inherent failures. Human erythropoeitin made by hamster cells has been sufficiently unlike the protein produced in the human body to cause critical immune reactions in some patients[10]; gene therapy trials have been dangerously uncertain and even fatal in their outcome; for every transgenic crop now widely grown in the United States, 99 failed examples of the same transformation have been discarded as "unsuitable"[11]; more than 90% of cloned animal embryos fail to survive, and the few surviving, like Dolly the sheep, die prematurely[12].

Despite these problems, the conceptual framework of molecular biology has remained unchanged since the 1950s. Thus, the *Time* cover story's illustrations, which have presumably been checked by a certified molecular biologist, are a virtual caricature of the

original Watson and Crick description of DNA self-duplication: Molecular models show the four DNA bases (which, in fact, should be nucleotides) propelled toward their proper complementary partners in the parental DNA strand, with a separate box to show that "the base pairs attach to each other with hydrogen bonds." Apparently, the mechanism first proposed by Watson and Crick fifty years ago to explain DNA 'self-replication' is, even today, accepted as the basic precept of molecular biology. This is further confirmed by a prominent DNA polymerase researcher, Myron Goodman, who has pointed out that since the 1950s "we have seen few challenges to the primacy of hydrogen bonding in the replication hierarchy." [13]

However, in another part of the forest, so to speak, of the vast terrain of DNA research, there are investigators, among them Myron Goodman, who in the last decade have put the concept of DNA self-duplication to the test of experiment. In 1991, Professor Goodman and several colleagues, publishing in *Annual Reviews of Biochemistry*, expressed "serious doubts about the importance of hydrogen bond contribution" to the fidelity of DNA replication, on the grounds that the bonds were energetically inadequate to distinguish between complementary and non-complementary free nucleotides[14]. In 1997, the dominant role of hydrogen bonding as the cause of DNA self-replication failed to meet an initial experimental test: It was shown that an analog of the natural thymine nucleotide, chemically modified to eliminate its capacity to form hydrogen bonds, is nevertheless not only incorporated by a DNA polymerase into DNA, but is also placed in its proper position opposite a template-borne adenine nucleotide[15]. Since the analog *does* resemble the natural thymine nucleotide in shape and size, this result suggested that geometry, rather than hydrogen bonding, accounted for the selection of the appropriate complementary nucleotides in polymerase-catalyzed DNA replication.

This clue has been pursued using new physico-chemical techniques, especially in x-ray crystallography and nuclear magnetic resonance, to bring the analysis of DNA replication down to the level of sub-molecular structure. Eric T. Kool of the Stanford University Department of Chemistry and Thomas A. Kunkel of the National Institutes of Environmental Health Sciences have recently reviewed much of the relevant research in *Annual Reviews of Biochemistry*[16, 17]. These studies have described the intimate relations among the participants in test tube DNA replication: the parental DNA template, the primer (the newly synthesized DNA strand), the free nucleotides added to it, and the DNA polymerase enzyme. Crystallographic analysis shows that a pocket is formed by a specific segment of the DNA polymerase protein, which includes the enzyme's biochemically "active site," together with a small section of the DNA template and the primer. The pocket is just the right size and shape to accommodate a free nucleotide, but only if that nucleotide makes the proper complementary pair with the adjacent template-borne nucleotide. Once the incoming free nucleotide is accepted into the pocket, a segment of the polymerase's protein structure is rearranged, which tightens the fit of the nucleotide pair within the pocket. This change in turn exposes the catalytic locus of the polymerase, which thereby induces the chemical reaction that links the new nucleotide to the end of the growing strand of complementary replicated DNA. A video of this molecular ballet is available on the website of Professor Joseph Kraut of the University of California, San Diego[18]. It shows that the hydrogen bond between the template-borne nucleotide and its incoming complementary partner is formed only *after* that free nucleotide has been accepted and closely fitted into the template/polymerase pocket.

At the end of this molecular choreography, the now-doubled DNA helix is equipped with the Watson-Crick hydrogen bonds between the template and the newly synthesized complementary DNA strand. But that is the *consequence* rather than the *cause* of DNA replication. That honor belongs *jointly* to the parental DNA template and the polymerase protein. Together, they form the walls of the pocket which, by its geometry, selects the properly complementary free nucleotides for DNA synthesis. Thus, even here, in the germinal event of biological inheritance - DNA replication - it is now evident that DNA is *not* the sole source of the genetic information embodied in the newly synthesized genome. Rather, that property is possessed jointly by DNA and the DNA polymerase protein.

Yet, to my knowledge, this conclusion -the inescapable outcome of an extensive series of physico-chemical studies- has not yet found its way into the literature of molecular genetics. As several of the field's leading researchers have complained, outmoded belief in the Watson-Crick hydrogen-bonding theory of DNA *self*-replication still "exists on the level of teaching paradigms."[15] Proof that this work has been ignored by molecular geneticists has appeared in a recent issue of *Nature* (Jan. 23, 2003). In an extensive series of articles to commemorate the discovery of the DNA double helix -"a modern icon"[19]- including one on the role of polymerase in DNA replication, there is no mention of this crucial research[20].

What can account for this surprising lapse in the normally avid interest of a vigorous area of research in such a new, meticulously documented and challenging discovery? A meaningful clue is provided by Crick's germinal 1958 paper, in which he proposed fundamental precepts that have governed the development of molecular genetics. One of these, the Sequence Hypothesis, which has since been well established by experiment, states that the gene's DNA nucleotide sequence codes for a protein's amino acid sequence. The second hypothesis, which Crick called the Central Dogma, states that "Once (sequential) information has passed into protein it cannot get out again." Although this precept has been assiduously adopted by molecular geneticists, in 1970 Crick attached to it an ominous warning: If even a single observation showed that genetic information *could* flow from protein to DNA, to RNA, or to another protein, "it would shake the whole intellectual basis of molecular biology."[21]

Crick apparently based this idea on the well-established fact that DNA's genetic information is encoded in a protein's amino acid sequence, which becomes inaccessible when that linear array is folded up into a three-dimensional ball-like structure. However, the biochemical activity of a protein, for example the catalytically active site of an enzyme, which actually gives rise to the genetic trait engendered by the protein, usually occurs on the surface of its folded structure. This fact alone conflicts with the notion that the enzyme's genetic information cannot "get out" of that molecule. After all, in Crick's scheme the genetic role of the enzyme is precisely to transmit the genetic information of its amino acid sequence to the chemical events that give rise to the inherited trait. But this can only occur through the passage afforded by the active site, which is a part of the protein's three-dimensional configuration.

Although it is not clear exactly how a protein's linear structure becomes folded into a specific three-dimensional configuration, evidently its amino acid sequence is a necessary -if sometimes a not sufficient- determinant of that process. Therefore, it follows that the catalytically "active site" on the enzyme's three-dimensional surface represents genetic

information that at least in part is derived from its amino acid sequence - which in turn is received from its gene's DNA. In the same way, the segment of the DNA polymerase's three-dimensional structure, which is necessary to the formation of the pocket that enforces the selection of the proper incoming nucleotide, is also a form of the polymerase protein's genetic information. Linked by the polymerase to the growing DNA primer strand, the newly acquired nucleotide contributes to the nucleotide sequence of the new DNA strand. Thus, the nucleotide sequence of the newly synthesized DNA - the cardinal example of genetic information - contains genetic information transferred from DNA polymerase, a protein. This is an explicit contradiction of Crick's Central Dogma.

Thus, the "intellectual basis of molecular biology" has indeed been shaken by this critical analysis of DNA replication, but neither the practitioners of that science, the biotechnologists who depend on it, nor the general public, who will suffer the consequences, appear to be aware of it.

The process of DNA replication so vividly dramatized in Professor Kraut's video exemplifies a curious irony. The course taken by molecular biology in the last 50 years is, of course, reductionist. A strenuous effort has been made to explain biology as an intricate form of molecular chemistry. Yet now that Professors Kool and Kraut and their colleagues have gone even further in the reductionist direction, and have given us a *sub*-molecular drama of DNA replication, in which even the roles of individual amino acids in the polymerase protein's structure are choreographed, the end result has the unmistakably anti-reductionist flavor of biology.

Here, I refer to my own reaction to Kunkel's visualization of the DNA polymerase-template pocket, with segments of the polymerase described (albeit somewhat fancifully) as a hand with its palm, thumb and fingers - the latter reaching toward the DNA of the parental template. It is not the anthropomorphic symbolism that brings biology into this sub-molecular picture; rather, it is the emergent creation of a new property - DNA replication - from the intimate physical interaction of DNA and the polymerase protein, neither of which, alone, possesses this capability.

In retrospect, it can be seen that the demise of the self-replicating DNA molecule was foreshadowed by earlier biochemical work that, following Kornberg's studies, has detected nearly twenty different DNA polymerases in a wide range of living things[16]. Certain of these enzymes, like Kornberg's original bacterial polymerase, carry out the initial template-supported synthesis of DNA from free nucleotides. In the test tube none of these polymerases come close to the Watson-Crick ideal of "exact" replication. As shown by the rate of spontaneous gene mutations, in living things DNA replication is indeed remarkably exact. The probability of a gene mutating - about one in 100,000 per cell division - is so low as to preclude an error rate in DNA replication of more than one wrongly placed constituent nucleotide in about ten billion. An initial DNA polymerase typically has an error rate of about one in ten thousand [16]- still a million times too great to meet the biologically required fidelity. The remaining errors are reduced to the required one in 10 billion by a group of "repair" enzymes - polymerases that detect, remove and properly replace the misplaced nucleotides or degrade heavily damaged sections of the newly synthesized DNA. The properties and functions of these enzymes vary considerably among different species[22]. The net result of such inter-species variation is that, as Goodman has pointed

out, "Different polymerases copying the same primer-template DNA can exhibit markedly different mutation frequencies and spectra [that is, types of mutations]."[23]

This phenomenon can convert an inter-species transgenic experiment into a genetic gamble. A gene that is faithfully replicated in its own species will undergo markedly more erratic replication when it is transferred into a new host with a different set of polymerase enzymes. Thus, in a recent study of rice containing a corn-derived transgene, it was concluded that "[T]he combined action of DNA repair and degradation enzymes on the introduced DNA gives rise to rearranged transgenic [nucleotide] sequences."[24]

The experimental evidence of DNA replication in transgenic organisms shows that the genetic information of the newly replicated transgene is in part derived from the new host's polymerase system. Given their separate evolutionary histories, the transgenic DNA and the host polymerase system are incongruent with regard to their respective influence on nucleotide selection. As a result, the high level of fidelity typical of DNA replication *within* both of the separate species breaks down in the transgenic organism.

In every species, evolution has been at work, long ago bringing the two participant parts of the replicative process - the DNA genes and the polymerase proteins that synthesize and repair them - into harmony. The polymerase's influence on the newly replicated DNA's nucleotide sequence and the influence of its gene on the polymerase's nucleotide selectivity are congruent, so that the biochemical specificity of both the DNA and the polymerase are faithfully reproduced and are stable over time.

Within any given species it is possible to argue that since the DNA encodes the polymerase protein, that enzyme cannot contribute any additional genetic information to the replication process. But this argument cuts both ways, for it is equally possible to say that the nucleotide sequence of the polymerase's gene was determined, in part, by the polymerase when that DNA was synthesized. Both of these statements represent an effort to derive a linear relationship from one that is not. Because the molecular mechanism of DNA replication is governed *jointly* by the DNA template and the polymerase, the relationship between their respective genetic information is circular: The biochemical specificity of the polymerase - its genetic information - is governed by its gene; and the nucleotide sequence of the gene's DNA - its genetic information - is influenced by the polymerase's biochemical specificity. As a result, the genetic information that flows in this circular pattern is necessarily a commingled mixture of influences from both the DNA and the polymerase system. In a transgenic organism, this mutual relation is disrupted by the evolutionary incompatibility of the two component parts, and their separate contributions to the overall process thereby become distinguishable.

All this is to say that the living cell is not merely a sack of chemicals, but a unique network of interacting components, dynamic yet sufficiently stable to survive. The living cell is made fit to survive by evolution; the marvelously intricate behavior of the nucleoprotein site of DNA synthesis is as much a product of natural selection as the bee and the buttercup. In moving DNA from one species to another, biotechnology has broken into the harmony that evolution produces, within and among species, over many millions of years of experimentation. Genetic modification is a process of very *unnatural* selection, a way to perversely reinvent the inharmonious arrangements that evolution has long ago discarded. The biotechnology industry has stood Darwin on his head.

It is a truism that in our society, such a new industry is created not for the purpose of enhancing scientific understanding, but in the hope of a competitive financial return. Unfortunately, the science on which biotechnology is founded has become, to a large extent, distorted in this process as well, and is itself in need of critical revision. If the science is to be redirected, and the unpredictable, uncontrolled experiment that is biotechnology is to be sent back to the laboratory where it rightly belongs, we will need to accept this task as our own and set Darwin back on his feet.

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**NOTE**
**Barry Commoner, Senior Scientist at the Center for the Biology of Natural Systems, Queens College, City University of New York, directs the CBNS Critical Genetics Project. Readers may obtain a list of references for the data cited in this article from the project website: www.criticalgenetics.org. This article is based in part on a presentation to The Gene Futures Conference, London, UK, February 11, 2003.**

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