Biologic Synthesis of Deoxyribonucleic Acid

An isolated enzyme catalyzes synthesis of this nucleic acid in response to directions from pre-existing DNA.

Arthur Kornberg

The knowledge drawn in recent years from studies of bacterial transformation (*1*) and viral infection of bacterial cells (*2*), combined with other evidence (*3*), has just about convinced most of us that deoxyribonucleic acid (DNA) is the genetic substance. We shall assume then that it is DNA which not only directs the synthesis of the proteins and the development of the cell but which must also be the substance which is copied so as to provide for a similar development of the progeny of that cell for many generations. Deoxyribonucleic acid, like a tape recording, carries a message in which there are specific instructions for a job to be done. Also, exact copies can be made from it, as from a tape recording, so that this information can be used again and elsewhere in time and space.

Are these two functions, the expression of the code (protein synthesis) and the copying of the code (preservation of the race), closely integrated or are they separable? What we have learned from our studies over the past 5 years is that the replication of DNA can be examined and at least partially understood at the enzymatic level even though the secret of how DNA directs protein synthesis is still locked in the cell.

Structure

First I should like to review very briefly some aspects of DNA structure which are essential for this discussion. Analysis of the composition of samples of DNA from a great variety of sources, and by many investigators (*4*), has revealed the remarkable fact that the purine content always equals the pyrimidine content. Among the purines, the adenine content may differ considerably from the guanine, and among the pyrimidines, the thymine from the cytosine. However, there is an equivalence of the bases with an amino group in the 6-position of the ring to the bases with a keto group in the 6-position. These facts were interpreted by Watson and Crick (*5*) in their masterful hypothesis of the structure of DNA. As shown in Fig. 1, they proposed in connection with their double-stranded model for DNA, discussed below, that the 6-amino group of adenine is linked by hydrogen bonds to the 6-keto group of thymine and that in a like manner guanine is hydrogen-bonded to cytosine, thus accounting for the equivalence of the purines to the pyrimidines.

On the basis of these considerations and the results of x-ray crystallographic measurements by Wilkins and his associates (*6*), Watson and Crick proposed a structure for DNA in which two long strands are wound about each other in a helical manner. Figure 2 is a diagrammatic representation of a fragment of a DNA chain about 10 nucleotide units long. According to physical measurements, DNA chains are, on the average, 10,000 units long. We see here the deoxypentose rings linked by phosphate residues to form the backbone of the chain; the purine and pyrimidine rings are the planar structures emerging at right angles from the main axis of the chain. Figure 3 is a more detailed molecular model (*7*) and gives a better idea of the packing of the atoms in the structure. The purine and pyrimidine bases of one chain are bonded to the pyrimidine and purine bases of the complementary chain by the hydrogen bonds described in Fig. 1.

The x-ray measurements have indicated that the space between the opposing chains in the model agrees with the calculated value for the hydrogen-bond linkage of a purine to a pyrimidine; it is too small for two purines and too large for two pyrimidines. Most rewarding from the biological point of view, the structure provides a useful model to explain how cellular replication of DNA may come about. For, if you imagine that these two chains separate and that a new chain is formed complementary to each of them, the result will be two pairs of strands, each pair identical to the original parent duplex and each member of the pair identical to the other.

Enzymatic Approach to Replication

Although we have in the Watson and Crick proposal a mechanical model of replication, we may at this point pose the question: What is the chemical mechanism by which this super molecule is built up in the cell? Some 60 years ago the alcoholic fermentation of sugar by a yeast cell was a "vital" process inseparable from the living cell, but through the Buchner discovery of fermentation in extracts and the march of enzymology during the first half of this century, we understand fermentation by yeast as a (now familiar) sequence of integrated chemical reactions.

Five years ago the synthesis of DNA was also regarded as a "vital" process. Some people considered it useful for biochemists to examine the combustion chambers of the cell, but tampering with the very genetic apparatus itself would surely produce nothing but disorder. These gloomy predictions were not justified then, nor are similar pessimistic attitudes justified now with regard to the problems of cellular structure and specialized function which face us. High adventures in enzymology lie ahead, and many of the explorers will come from the training fields of carbohydrate, fat, amino acid, and nucleic acid enzymology.

I feel now, as we did then, that for an effective approach to the problem of nucleic acid biosynthesis it is essential

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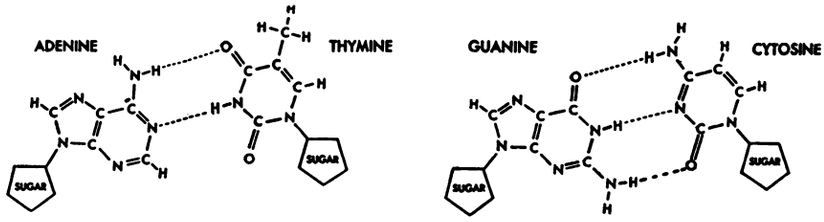

Fig. 1. Hydrogen bonding of bases.

to understand the biosynthesis of the simple nucleotides and the coenzymes and to have these concepts and methodology well in hand. It was from these studies that we developed the conviction that an activated nucleoside 5′-phosphate is the basic biosynthetic building block of the nucleic acids (*8*). You will recall that the main pathways of purine and pyrimidine biosynthesis all lead to the nucleoside 5′-phosphate (*8*); they do not usually include the free bases or nucleosides, except as salvage mechanisms. While the 2′ and 3′ isomers of the nucleotides are known, they probably arise mainly from certain types of enzymatic degradation of the nucleic acids. You will also recall from the biosynthesis of coenzymes (*9*), the simplest of the nucleotide condensation products, that it is adenosine triphosphate (ATP) which condenses with nicotinamide mononucleotide to form diphosphopyridine nucleotide, with riboflavin phosphate to form flavine adenine dinucleotide (FAD), with pantetheine phosphate to form the precursor of coenzyme A, and so forth. This pattern has been amplified by the discovery of identical mechanisms for the activation of fatty acids and amino acids, and it has been demonstrated further that uridine, cytidine, and guanosine coenzymes are likewise formed from the respective triphosphates of these nucleosides.

This mechanism (Fig. 4), in which a nucleophilic attack (*10*) on the pyrophosphate-activated adenyl group by a nucleoside monophosphate leads to the formation of a coenzyme, was adopted as a working hypothesis for studying the synthesis of a DNA chain. As illustrated in Fig. 5, it was postulated that the basic building block is a deoxynucleoside 5′-triphosphate which is attacked by the 3′-hydroxyl group at the growing end of a polydeoxynucleotide chain; inorganic pyrophosphate is eliminated, and the chain is lengthened by one unit. The results of our studies of DNA synthesis, as is shown below, are in keeping with this type of reaction.

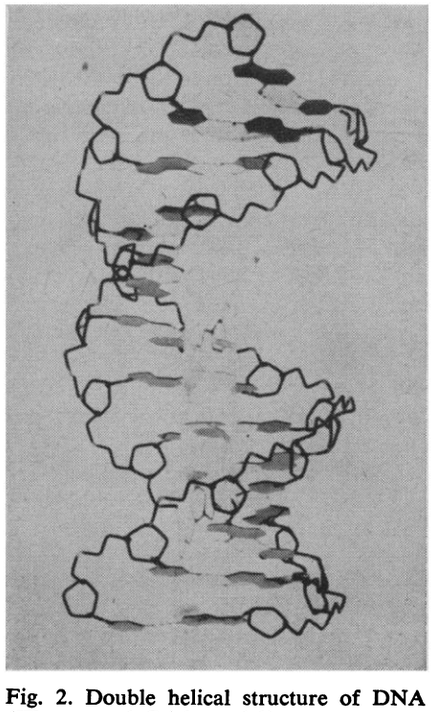

Fig. 2. Double helical structure of DNA (Watson and Crick model).

Properties of the Enzyme

First let us consider the enzyme and comment on the way in which it was discovered (*8, 11*). Mixing the triphosphates of the four deoxynucleosides which commonly occur in DNA with an extract of thymus or of bone marrow or of *Escherichia coli* would not be expected to lead to the net synthesis of DNA. Instead, as might be expected, the destruction of DNA by the extracts of such cells and tissues was by far the predominant process, and one had to resort to more subtle devices to detect such a biosynthetic reaction. We used a C^{14}-labeled substrate of high specific radioactivity and incubated it with adenosine triphosphate and extracts of *Escherichia coli*, an organism which reproduces itself every 20 minutes. The first positive results represented the conversion of only a very small fraction of the acid-soluble substrate into an acid-insoluble fraction (50 or so counts out of a million added). While this represented only a few micromicromoles of reaction, it was something. Through this tiny crack we tried to drive a wedge, and the hammer was enzyme purification (*12*).

This has been and still is a major preoccupation. Our best preparations are several thousand-fold enriched with respect to protein over the crude extracts, but there are still contaminating quantities of one or more of the many varieties of nuclease and diesterase present in the *E. coli* cell. The occurrence of what appears to be a similar DNA-synthesizing system in animal cells as well as in other bacterial species has been observed (*13*). We must wait

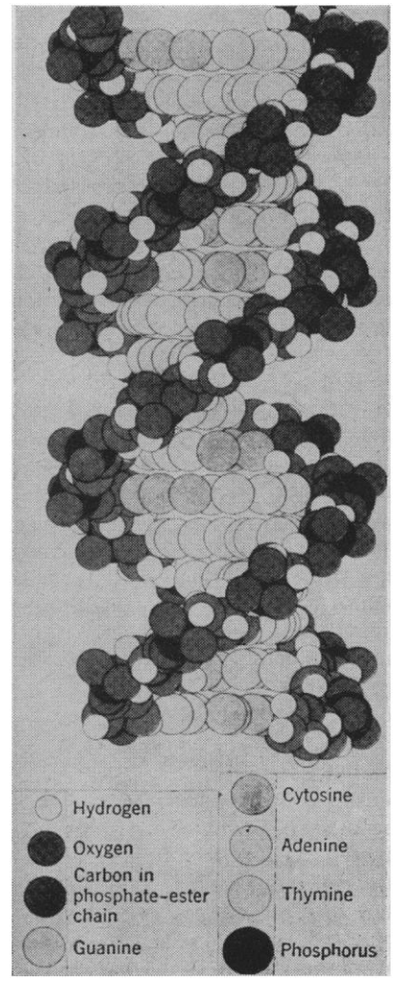

Fig. 3. Molecular model of DNA [After M. Feughelman *et al.* (*7*)]

for purification of the enzymes from these sources in order to make valid comparisons with the *E. coli* system.

The requirements for net synthesis of DNA with the purified *E. coli* enzyme (*14*) are shown in the equation in Fig. 6. All four of the deoxynucleotides which form the adenine-thymine and guanine-cytosine couples must be present. The substrates must be the tri- and not the diphosphates, and only the deoxy sugar compounds are active. Deoxyribonucleic acid, which must be present, may be obtained from animal, plant, bacterial, or viral sources, and the best indications are that all these DNA samples serve equally well in DNA synthesis provided their molecular weight is high. The product, which I discuss below in further detail, accumulates until one of the substrates is exhausted and may be 20 or more times greater in amount than the DNA added, and thus is composed to the extent of 95 percent or more of the substrates added to the reaction mixture. Inorganic pyrophosphate is released in quantities equimolar to the deoxynucleotides converted to DNA.

Should one of these substrates be omitted, the extent of the reaction is diminished by a factor of more than 10^4, and special methods are then required to detect it. It turns out that when one of the deoxynucleotide substrates is lacking, an extremely small yet significant quantity of nucleotide is linked to the DNA primer. My co-workers and I have described this so-called "limited reaction" (*15*) and have shown that under these circumstances a few deoxynucleotides are added to the nucleoside ends of some of the DNA chains but that further synthesis is blocked for lack of the missing nucleotide. Current studies suggest that this limited reaction represents the repair of the shorter strand of a double helix in which the strands are of unequal length, and that the reaction is governed by the hydrogen-bonding of adenine to thymine and of guanine to cytosine.

When all four triphosphates are present, but when DNA is omitted, no reaction takes place at all. What is the basis for this requirement? Does the DNA function as a primer in the manner of glycogen, or does it function as a template in directing the synthesis of exact copies of itself? We have good reason to believe that it is the latter, and as the central and restricted theme of this article, I should like to emphasize that

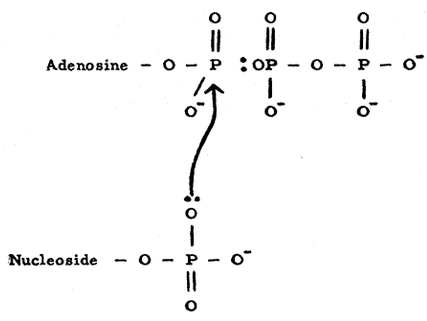

Fig. 4. Nucleophilic attack of a nucleoside monophosphate on ATP.

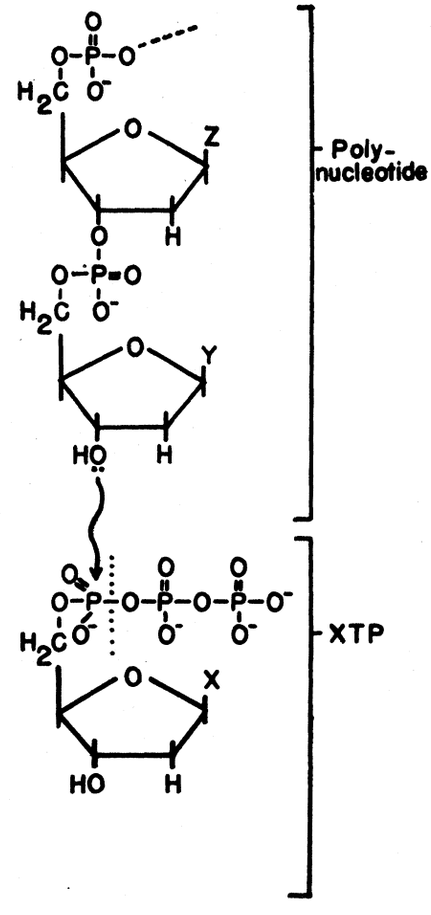

Fig. 5. Postulated mechanism for extending a DNA chain.

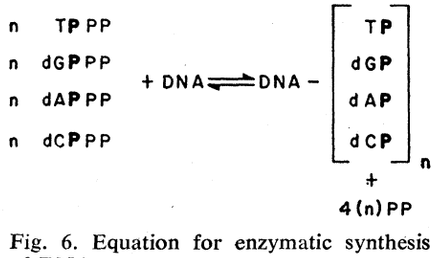

Fig. 6. Equation for enzymatic synthesis of DNA.

it is the capacity for base pairing by hydrogen-bonding between the preexisting DNA and the nucleotides added as substrates that accounts for the requirement for DNA.

The enzyme we are studying is thus unique in our experience to date in that it takes directions from a template—it adds the particular purine or pyrimidine substrate which will form a hydrogen-bonded pair with a base on the template (Fig. 7). There are five major lines of evidence that support this thesis.

Physical Properties of Enzymatically Synthesized DNA

The first line of evidence is derived from studies of the physical nature of the DNA produced by the enzyme. I might mention again that in these descriptions as in those of the chemical nature of DNA, discussed below, 90 to 95 percent of the DNA sample comes from the substrates used in the reaction. From collaborative studies with Howard K. Schachman, to whom we are greatly indebted, it can be said that the enzymatic product is indistinguishable from high-molecular-weight, double-stranded DNA isolated from natural sources (*16*). It has sedimentation coefficients in the neighborhood of 25 and reduced viscosities of 40 deciliters per gram, and on the basis of these measurements we believe it to be a long, stiff rod with a molecular weight of about 6 million. When the DNA is heated, the rod collapses and the molecule becomes a compact, randomly coiled structure; it may be inferred that the hydrogen bonds holding the strands together have melted, and this is borne out by characteristic changes in the viscometric and optical properties of the molecule. Similar results are found upon cleavage of the molecule by pancreatic deoxyribonuclease. In all these respects the enzymatically synthesized DNA is indistinguishable from the material isolated from natural sources and may thus be presumed to have a hydrogen-bonded structure similar to that possessed by natural DNA.

Would one imagine that the collapsed, jumbled strands of heated DNA would serve as a primer for DNA synthesis? Very likely one would think not. Guided by everyday experience with a jumbled strand of twine, one might

regard this as a hopeless template for replication. It turns out that the collapsed DNA is an excellent primer and that the nonviscous, randomly coiled, single-stranded DNA leads to the synthesis of highly viscous, double-stranded DNA (*17*). Sinsheimer has isolated from the tiny ΦX174 virus a DNA which appears to be single-stranded (*18*). Like heated DNA, it has proved to be an excellent primer (*17*) and a useful material in current studies (*19*) for demonstrating in density-gradient sedimentations its progressive conversion to a double-stranded condition during the course of enzymatic synthesis.

While a detailed discussion of the physical aspects of replication is not feasible in this article, it should be mentioned that the DNA in the single-stranded condition is not only a suitable primer but is the only active form when the most purified enzyme preparations are used. With such preparations of *E. coli,* the native, double-stranded DNA is inert unless it is heated or pretreated very slightly with deoxyribonuclease. Bollum has made similar observations with the enzyme that he has purified from calf thymus (*20*).

Substitution of Analogs

The second line of evidence is derived from studies of the activity of the substrates when substitutions are made in the purine and pyrimidine bases. From the many interesting reports on the incorporation of bromouracil (*21*), azaguanine (*22*), and other analogs into bacterial and viral DNA, it might be surmised that some latitude in the structure of the bases can be tolerated provided there is no interference with their hydrogen bondings. When experiments were carried out with deoxyuridine triphosphate or 5-bromodeoxyuridine triphosphate, it was found that these compounds supported DNA synthesis when used in place of thymidine triphosphate but not when substituted for the triphosphates of deoxyadenosine, deoxyguanosine, or deoxycytidine. As already described (*23*), 5-methyl- and 5-bromocytosine specifically replaced cytosine; hypoxanthine substituted only for guanine; and, as just mentioned, uracil and 5-bromouracil specifically replaced thymine. These findings are best interpreted on the basis of hydrogen bonding of the adenine-thymine and guanine-cytosine type.

Along these lines it is relevant to

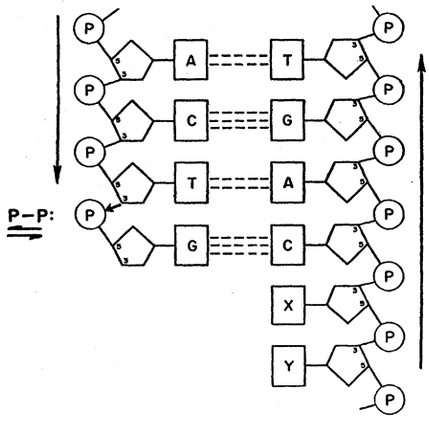

Fig. 7. Mechanism for enzymatic DNA replication.

mention the existence of a naturally occurring "analog" of cytosine, hydroxymethyl cytosine (HMC), which is found in place of cytosine in the DNA of the *E. coli* bacteriophages of the T-even series (*24*). In this case the DNA contains equivalent amounts of HMC and guanine and, as usual, equivalent amounts of adenine and thymine. Of additional interest is the fact that the DNA's of T2, T4, and T6 bacteriophages contain glucose linked to the hydroxymethyl groups of the HMC in characteristic ratios (*25, 26*), although it is clear that in T2 and T6 some of the HMC groups contain no glucose (*26*).

These characteristics have posed two problems regarding the synthesis of these DNA's which might appear to be incompatible with the simple base-pairing hypothesis. First, what mechanism is there for preventing the inclusion of cytosine in a cell which under normal conditions has deoxycytidine triphosphate and incorporates it into its DNA? Second, how does one conceive of the origin of the constant ratios of glucose to HMC in DNA if the incorporation occurs via glucosylated and nonglucosylated HMC nucleotides? Our recent experiments have shown that the polymerase reaction in the virus-infected cell is governed by the usual hydrogen-bonding restrictions but with the auxiliary action of several new enzymes developed specifically in response to infection with a given virus (*27, 28*). Among the new enzymes is one which splits deoxycytidine triphosphate and thus removes it from the sites of polymerase action (*28*). Another is a type of glucosylating enzyme that transfers glucose from uridine diphosphate glucose directly and specifically to certain HMC residues in the DNA (*28*).

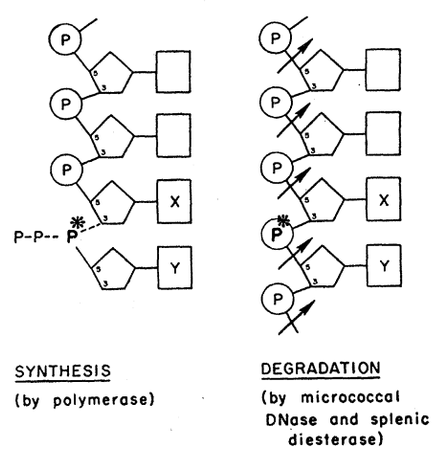

Fig. 8. Method for determining sequences in DNA.

Chemical Composition

The third line of evidence is supplied by an analysis of the purine and pyrimidine base composition of the enzymatically synthesized DNA. We may ask two questions. First, will the product have the equivalence of adenine to thymine and of guanine to cytosine that characterize natural DNA? Second, will the composition of the natural DNA used as primer influence and determine the composition of the product? In Table 1 are the results which answer these two questions (*29*). The experiments are identical except that in each case a different DNA primer was used: *Mycobacterium phlei, Escherichia coli,* calf thymus, and phage T2 DNA, respectively.

In answer to the first question, it is clear that in the enzymatically synthesized DNA, adenine equals thymine and guanine equals cytosine, so the purine content is in every case identical to the pyrimidine. In answer to the second question, it is again apparent that the characteristic ratio of adenine-thymine pairs to guanine-cytosine pairs of a given DNA primer is imposed rather faithfully on the product that is synthesized. Whether the net DNA increase is only 1 percent, as measured with isotopic tracers, or 1000 percent, the results are the same.

It can be said further that it has not been possible to distort these base ratios by using widely differing molar concentrations of substrates or by any other means. In the last line of Table 1 is a rather novel "DNA" which is synthe-

sized under conditions that I will not describe here (*17, 30*). Suffice it to say that after very long lag periods, a copolymer of deoxyadenylate and thymidylate (A-T) develops which has the physical size and properties of natural DNA and in which the adenine and thymine are in a perfectly alternating sequence. When this rare form of DNA-like polymer is used as a primer, new A-T polymer synthesis starts immediately, and even though all four triphosphates are present, no trace of guanine or cytosine can be detected in the product. The conclusion thus seems inescapable that the base composition is replicated in the enzymatic synthesis and that hydrogen-bonding of adenine to thymine and of guanine to cytosine is the guiding mechanism.

Enzymatic Replication of Nucleotide Sequences

The fourth line of evidence which I should like to cite is drawn from current studies of base sequences in DNA and their replication. As I have suggested already, we believe that DNA is the genetic code; the four kinds of nucleotides make up a four-letter alphabet, and their sequence spells out the message. At present we do not know the sequence; what Sanger has done for peptide sequence in protein remains to be done for nucleic acids. The problem is more difficult, but not insoluble.

Our present attempts at determining the nucleotide sequences (*31*) will be described in detail elsewhere, and I will only summarize them here. Deoxyribonucleic acid is enzymatically synthesized, with phosphorus-32 as label, in one of the deoxynucleoside triphosphates; the other three substrates are unlabeled. This radioactive phosphorus, attached to the 5-carbon of the deoxyribose, now becomes the bridge between that substrate molecule and the nucleotide at the growing end of the chain with which it has reacted (Fig. 8). At the end of the synthetic reaction (after some 10^{16} diester bonds have been formed), the DNA is isolated and digested enzymatically to yield the 3′-deoxynucleotides quantitatively. It is apparent (Fig. 8) that the phosphorus atom formerly attached to the 5-carbon of the deoxynucleoside triphosphate substrate is now attached to the 3-carbon of the nucleotide with which it reacted during the course of synthesis of the DNA chains. The phosphorus-32 content of each of the 3′-deoxynucleotides, isolated by paper electrophoresis, is a measure of the relative frequency with which a particular substrate reacted with each of the four available nucleotides in the course of synthesis of the DNA chains. This procedure, when carried out four times with a different labeled substrate in each case, yields the relative frequencies of all the 16 possible kinds of dinucleotide (nearest neighbor) sequences.

Such studies have, to date, been carried out with DNA primer samples from six different natural sources. The conclusions are as follows: (i) All 16 possible dinucleotide sequences are found in each case; (ii) the pattern of relative frequencies of the sequences is unique and reproducible in each case and is not predicted from the base composition of the DNA; (iii) enzymatic replication involves base pairing of adenine to thymine and of guanine to cytosine; and, most significantly (iv) the frequencies also indicate clearly that the enzymatic replication produces two strands of opposite direction, as predicted by the Watson and Crick model.

These studies and anticipated extensions of them should yield the dinucleotide frequencies of any DNA sample which can serve as an effective primer for enzymatic replication and thus provide some clues for deciphering the DNA code. Unfortunately, this method does not provide information about trinucleotide frequencies, but we are hopeful that, with the improvement of enzymatic tools for analysis and chromatographic techniques for isolation, some start can be made in this direction.

Requirement for Four Triphosphates and DNA for DNA Synthesis

Returning to the earlier-stated requirement for all four deoxynucleoside triphosphates and DNA for DNA synthesis, we can now regard and understand this requirement as another and final line of evidence for hydrogen bonding. Without added DNA there is no template for hydrogen bonding, and without all four triphosphates, synthesis stops early and abruptly for lack of a hydrogen-bonding mate for one of the bases in the template.

Summary

I have sketched the enzymatic approaches to the problem of DNA replication and the properties of the DNA-synthesizing enzyme purified from *Escherichia coli*. The unifying and basic generalization about the action of this enzyme 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 to thymine and of guanine to cytosine. The experimental basis for this conclusion is derived from the observations of: (i) the double-stranded character of the enzymatically synthesized DNA and its origin from a single-stranded molecule, (ii) the pattern of substitution of analogs for the naturally occurring bases, (iii) the replication of the chemical composition, (iv) the replication of the nucleotide (nearest neighbor) sequences and the antiparallel direction of the strands, and (v) the requirement for all four deoxynucleoside triphosphates (adenine, thymine, guanine, and cytosine) and for DNA for DNA synthesis (*32*).

Table 1. Chemical composition of enzymatically synthesized DNA, synthesized with different primers. *A*, adenine; *T*, thymine; *G*, guanine; *C*, cytosine.

DNA	A	T	G	C	$\frac{A+G}{T+C}$	$\frac{A+T}{G+C}$
Mycobacterium phlei						
Primer	0.65	0.66	1.35	1.34	1.01	0.49
Product	0.66	0.65	1.34	1.37	0.99	0.48
Escherichia coli						
Primer	1.00	0.97	0.98	1.05	0.98	0.97
Product	1.04	1.00	0.97	0.98	1.01	1.02
Calf thymus						
Primer	1.14	1.05	0.90	0.85	1.05	1.25
Product	1.12	1.08	0.85	0.85	1.02	1.29
Bacteriophage T2						
Primer	1.31	1.32	0.67	0.70	0.98	1.92
Product	1.33	1.29	0.69	0.70	1.02	1.90
A-T copolymer	1.99	1.93	<0.05	<0.05	1.03	40

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32. Any credit for the work cited here is shared by my colleagues in New York, Bethesda, St. Louis, and Stanford, and by the whole international community of chemists, geneticists, and physiologists, which is truly responsible for the progress in nucleic acid biochemistry.

Science in the News

Scientists in Government: Growing Concern Over Conflicts of Interest

There is considerable and growing concern over the position of scientists with regard to the conflict of interest laws. The subject is talked of a good deal in private but only rarely in public, a situation which reflects the delicacy with which it is felt this potentially explosive issue must be handled.

The relevant laws are a group of seven poorly defined, vaguely interpreted statutes which, in their broadest interpretation, prohibit anyone working for the government from having a financial interest in any group having dealings with the government. They tend to put almost anyone working for the government on less than a career civil service basis in an extremely awkward position. The situation is difficult for administrative and legal personnel, often preventing the government from obtaining the services of an outstanding man because of the unreasonable financial sacrifices he would have to make in order to protect himself from a possible accusation of violating the law. But nowhere is the situation more touchy than in the case of scientific personnel.

The government today relies on an intricate web of consultancies, contracts, and part-time and temporary employees to provide itself with the scientific and technical assistance it must have. It underwrites more than half the scientific research done in this country. It "employs" in some fashion a very large fraction of the leading scientists in the country, and a question of conflicts of interest could be raised in almost every case. The institution or corporation with which the scientist is associated very probably is receiving a share of the more than $5 billion the government spends annually on scientific work. Quite often it is doing work for the government in precisely the area in which the scientist is being asked to advise the government.

Conflicts Unavoidable

The situation is awkward, but it is also absolutely unavoidable. The government clearly needs the best scientific advice it can get, and it can get this advice only from men with the pertinent experience—that is, in most cases, precisely from the men who will find themselves in a conflict-of-interest situation. The problem is complicated further because many of these men will not only be associated with a group doing business with the government in the area in which they are to serve, but they will also be serving, in addition, as consultants to one or more other corporations or institutions which, again, are doing business with the government in the area in which the scientist is asked to advise the government. And to complicate the picture still further, a significant and growing fraction of these scientists own stock, and sometimes large blocks of stock, in the "space age" research corporations that have sprung up in intellectual centers throughout the country.

New York Bar Study

The entire conflict-of-interest problem has been studied by a committee