GENES AND CHROMOSOMES

J. R. Lloyd

DIMENSIONS OF SCIENCE
Series Editor: Professor Jeff Thompson

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M.A.(Oxon)

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Series Editor's Preface

This book is one in a Series designed to illustrate and explore a range of ways in which scientific knowledge is generated, and techniques are developed and applied. The volumes in this Series will certainly satisfy the needs of students at 'A' level and in first-year higher-education courses, although there is no intention to bridge any apparent gap in the transfer from secondary to tertiary stages. Indeed, the notion that a scientific education is both continuous and continuing is implicit in the approach which the authors have taken.

Working from a base of 'common core' 'A'-level knowledge and principles, each book demonstrates how that knowledge and those principles can be extended in academic terms, and also how they are applied in a variety of contexts which give relevance to the study of the subject. The subject matter is developed both in depth (in intellectual terms) and in breadth (in relevance). A significant feature is the way in which each text makes explicit some aspect of the fundamental processes of science, or shows science, and scientists, 'in action'. In some cases this is made clear by highlighting the methods used by scientists in, for example, employing a systematic approach to the collection of information, or the setting up of an experiment. In other cases the treatment traces a series of related steps in the scientific process, such as investigation, hypothesising, evaluating and problem-solving. The fact that there are many dimensions to the creation of knowledge and to its application by scientists and technologists is the title and consistent theme of all the books in the Series.

The authors are all authorities in the fields in which they have written, and share a common interest in the enjoyment of their work in science. We feel sure that something of that satisfaction will be imparted to their readers in the continuing study of the subject.

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Contents

1 Genes: Their Main Features

Genes are made of DNA or RNA. Information is stored in genes as a linear directional sequence of four bases. This can be translated into protein by reading the bases in groups of three, or 'triplets'. Each triplet is translated into one amino acid by a widely used code. The sequence of bases thus determines the order of amino acids in the protein. The proteins made are often enzymes and thus have a major effect on cell metabolism. Those that are not enzymes regulate the activities of other genes. Other proteins form structures such as hair, or are contractile. Some genes do not code for protein, but produce RNA molecules which have their own special roles, such as 'ribosomal RNA' (rRNA) or 'transfer RNA' (tRNA). Genes can reproduce or 'replicate' themselves, and are thereby inherited.

Genes are most remarkable for their constancy. Copies of some genes have been replicated millions of times and conserved by natural selection for millions of years. This constancy is not absolute. Very rarely mistakes are made in replication which alter the sequence of bases – a process called 'mutation'. This is the ultimate source of new characteristics. The new gene can be recombined with others arising in the same way. Inaccuracy of replication, even at this very low rate, is essential to allow organisms to adapt to new or local conditions. Sequence changes are the ultimate source of genetic variation for evolution.

To sum up, genes

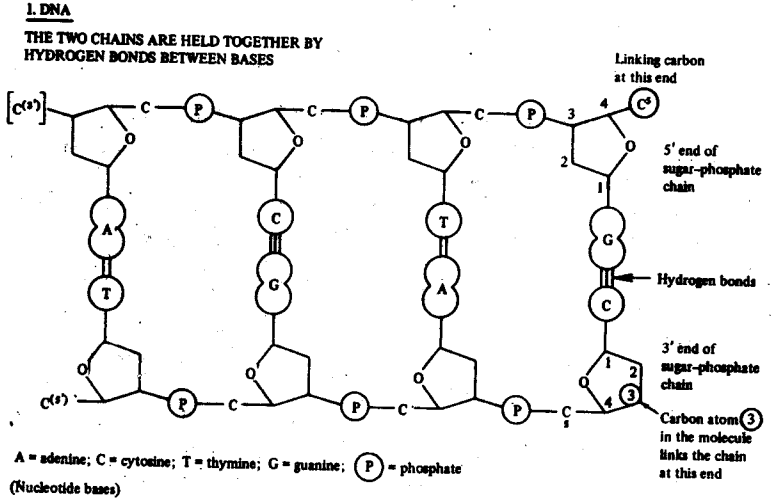
are made of DNA or RNA
have a sequence that can determine proteins
can be regulated by the products of other genes
are accurately replicated
can mutate or change their sequence.

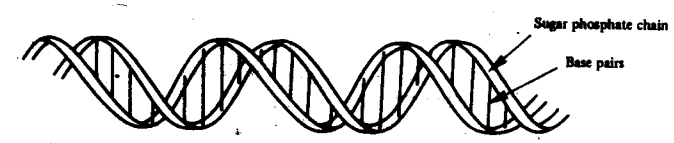
In this chapter the most basic features of genes will be described

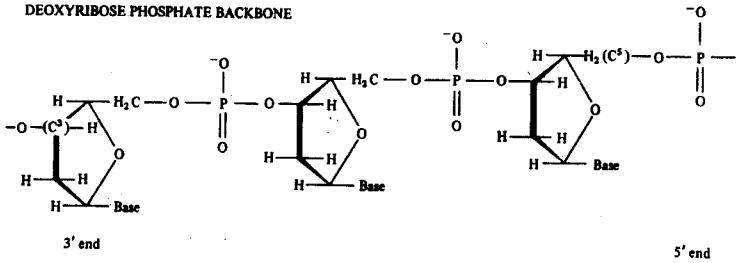
their chemical structure, and
their two main functions – replication and protein synthesis.

CHEMICAL STRUCTURE OF GENES

This is best grasped by considering the diagrams in figures 1.1 and 1.2, but there are some aspects of the structure which should be especially noted.







FOUR POSSIBLE BASES

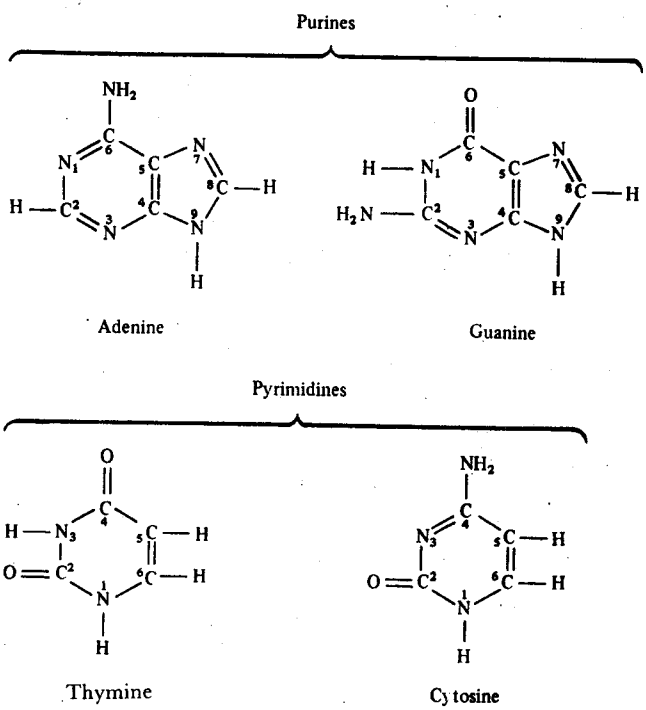
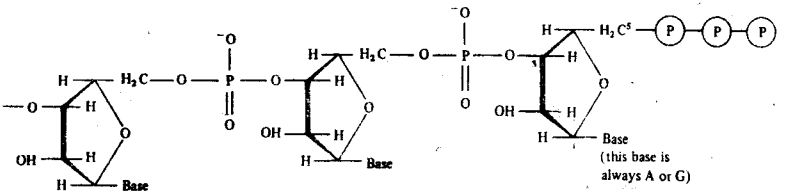


Figure 1.1 *Deoxyribonucleic acid, DNA.*

II. RNA

Ribonucleic acid (as in messenger RNA)

THE SUGAR-PHOSPHATE CHAINS

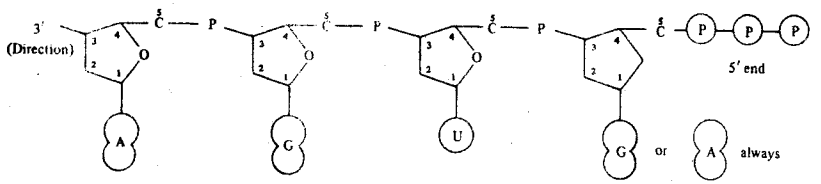


3′ end

5′ end

Note: The OH at carbon atom 2 is only H in DNA (hence deoxy-)

RNA – WITH BASES ATTACHED



RNA is found as single chains only.

FOUR POSSIBLE BASES

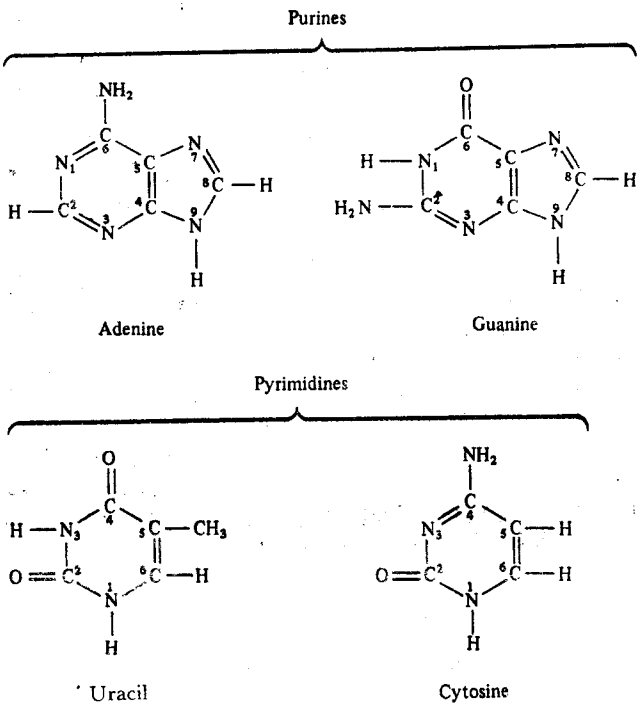


Figure 1.2 *Ribonucleic acid (as in messenger RNA).*

1. The sugar–phosphate chains, though identical throughout the length of the molecules, do have a direction. One end of the molecule has a free 5′ carbon attached to three phosphate groups, the other has a free 3′ carbon with a hydroxyl group attached (figure 1.2). Both replication and the transcription of mRNA proceed in the 5′ to 3′ direction. The evidence for this comes from the following experiment. If a rapidly transcribing gene is kept in the environment of a large amount of radioactively labelled phosphate, the ratio of ^{32}P to nucleotide is highest (3 : 1) at the beginning of synthesis, and decreases progressively with time (figure 1.3).

Because one strand of a double helix has its 5′–3′ sugar chain running the opposite way to the other strand (anti-parallel), this growth of

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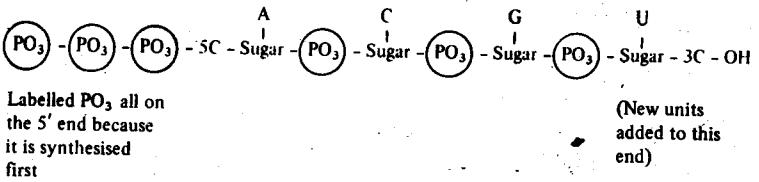


Figure 1.3 -

new DNA chains or mRNA means that movement along the strand being copied (the template) is in a 3′ to 5′ direction (figure 1.4).

The same principle is used to give direction when a messenger RNA molecule is translated by a ribosome. The ribosome moves along the mRNA in the 5′ to 3′ direction. This implies that only one strand in the DNA within any one gene is used to make mRNA. If the starting point for copying is determined, then only one strand can get copied. The other strand with its complementary bases is unlikely to make sense whichever direction of reading is used. The sugar chain polarity thereby prevents useless mRNA being formed.

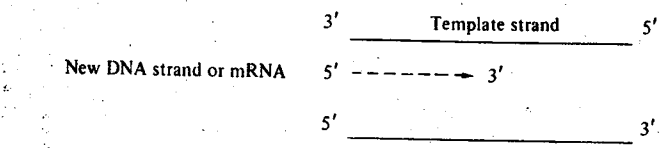


Figure 1.4

2. The discovery that the DNA molecule always has its bases paired in only one way, C with G and T with A, explained the earlier findings of Chargaff. He had shown that the proportion of G to C and of T to A were constant. This arrangement of the bases also provides a vital clue to the mechanism of replication – that is, use of a template or mould on which to fit a replica (figure 1.5).
3. The order of the four bases is unique for any one gene. There is no chemical restriction on the sequence of bases in a gene. Their order is determined by biological selection for functional sequences from patterns which have arisen in the past by chance.

4. DNA is normally found in some form of helix, with the two strands twisted round one another, and the bases appearing like steps in a spiral staircase. There are three forms which are of biological importance.

'A' DNA. This is a right-handed helix with about 11 bases per turn. It is found in DNA gels containing relatively little water.

'B' DNA. A right-handed helix with about 10 bases per turn, the planes of the bases being perpendicular to the axis of the helix. This is the form originally modelled by Watson and Crick and is thought to be the most common arrangement for chromosomal DNA.

'Z' DNA. This is left-handed and has about 12 bases per turn. It may be of significance in gene activation in eukaryotes.

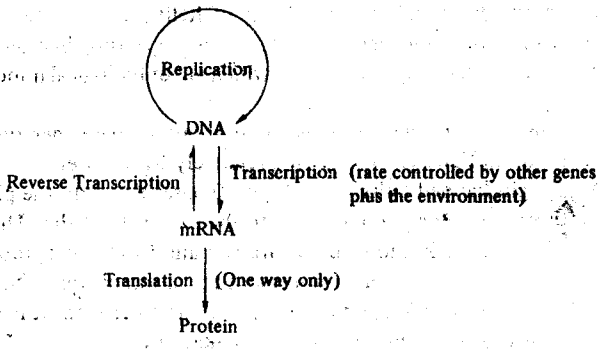
It may well be that the classical notion of DNA being a fixed and somewhat stable structure needs to be revised, and that there is a much more dynamic conversion of one form into the other, these transitions being related to the activity of the gene. Further discussion on this point will be found in chapter 5.

5. Whether the DNA is in the A, B or Z form, the whole helix may be wound into further spirals (supercoils) and may also form loops and kinks within the chromosome. These spirals made of spirals are explored in some detail in chapter 5.
6. Looking at the sugar-phosphate backbone again, it should be realised that the phosphates make the whole molecule acidic. To form one type of supercoil the DNA is wound round proteins called histones which have large amounts of the basic amino acids lysine and arginine in them, and therefore interact strongly with the acidic DNA.
7. The techniques of finding the sequence of bases in DNA have undergone a revolution in the last ten years. One method is described in appendix A. It relies on the amazing discovery that chains of DNA which differ in length from one another by only one base pair can be separated into discrete bands by exploiting their ability to travel through a gel at different speeds. The chain fragments are drawn through the gel by electric charge, a technique known as 'electrophoresis'.

MAIN FUNCTIONS OF GENES

Replication

Right at the heart of the process of reproduction in organisms lies the ability of both chains of the DNA molecule to act as templates or moulds



for others, because of the specificity of the A-T and C-G pairings (see figure 1.5). Replication is semiconservative – that is, each of the two parent strands gets a new strand attached to it in the process. See figure 1.5.

In 1958 Meselson and Stahl demonstrated this very effectively using the bacterium *Escherichia coli*. Their technique is described in detail in appendix B, and should be carefully noted.

The chemical events of DNA replication have been much studied in *E. coli*. It is likely that similar principles are used in eukaryotes, but it is possible that the process is more complex.

Firstly, the chains must be unwound and separated from each other. This does not start from one end and proceed steadily down to the other, but starts at many places in eukaryotes. In prokaryotes replication starts at only one site, and works its way right round the circular DNA both ways. See figure 1.6.

Unwinding

This is catalysed by an enzyme called helicase, and is very fast – about 100 revolutions per second. As each replicon unwinds it causes supercoiling to one side, which must eventually be removed if the two strands are to separate. In bacteria the supercoil spreads around the circular DNA and is removed by topoisomerase I, (the nicking-closing enzyme). In eukaryotes it is not known where the release of the supercoils occurs but it is likely that there has to be a release process between each loop, and there are many loops per chromosome. See figure 1.7.

New bases are attached to the old strands' bases by complementary pairing, and then joined up to each other lengthways by a new sugar-

The Principle of the Template or Mould process of Replication

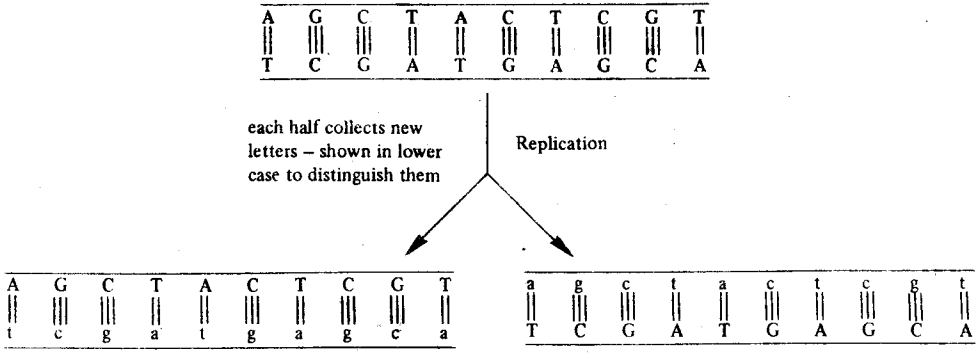
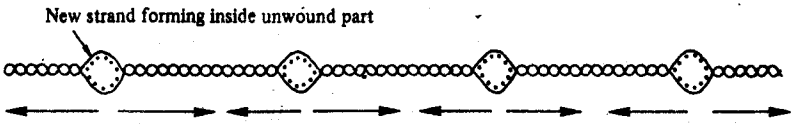


Figure 1.5



The loops spread until they all connect. Each fully developed loop is one replicon

Figure 1.6

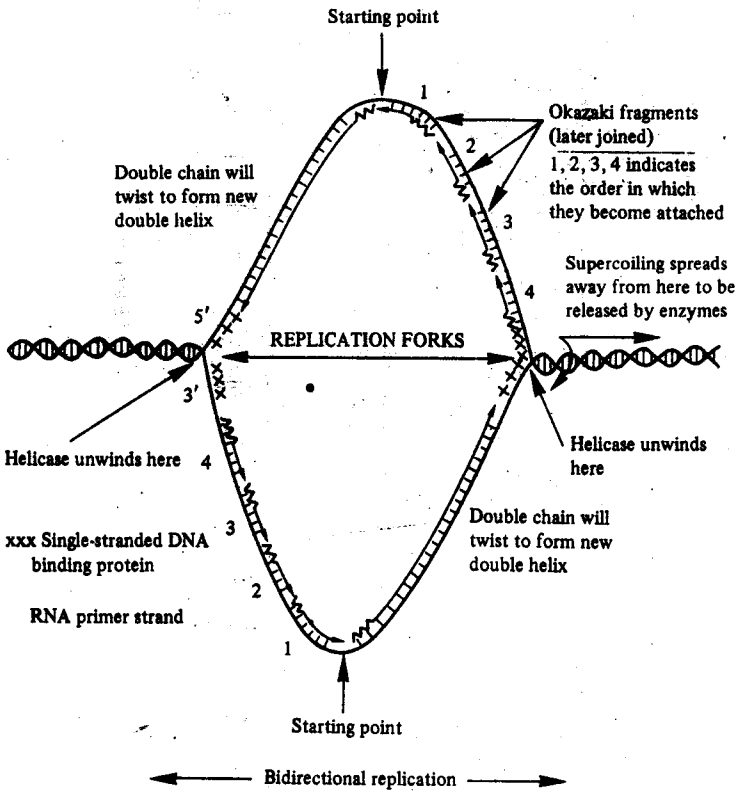


Figure 1.7 *DNA replication.*

phosphate backbone. The formation of this new chain of repeating molecules is called *polymerisation*. There are several enzyme complexes, called *polymerases*, which catalyse this process. Some of them also catalyse hydrolyses, which remove bases. In prokaryotes DNA replication is several orders of magnitude more accurate than RNA production. The error rate is only about 1 per 10^{10} base pairs copied. This is achieved by a double check system. The DNA polymerase normally does not continue to add bases unless each fits properly into complementary pairs, and also the base pair that has just been fitted is checked, and will be removed by hydrolysis if it is incorrect. Because of the need for this check, a completely new start to a strand of DNA cannot be made if there is no base pair in position to be checked. In order to start the process an RNA 'primer' is synthesised first; this uses RNA polymerase, which does not search for the last base fitted and check if it is correct, and so a *new* chain can be started. After this short stretch of temporary primer is formed, the DNA polymerase takes over. Later the stretch of RNA is removed, being recognised by its ribose instead of deoxyribose backbone sugar. It is hydrolysed away by an RNAase, and DNA put in its place by DNA polymerase.

In eukaryotes the double check DNA polymerase is not used, possibly because of the inaccessibility of the DNA wound on the proteins or because of the high energy cost with large gemones, and this may account for the higher mutation rate which has been recorded for eukaryotes. Evidence that repair and checking systems are active, even after synthesis, comes from the uracil removal system which recognises uracil as foreign to DNA. Cytosine spontaneously deaminates to form uracil at a low, but measurable rate. This would form mutations because U then pairs with an A rather than with a G like the C from which it was formed. The uracil is removed by hydrolysis by uracil DNA glycosylase. This leaves a space in one strand. An endonuclease responds to this defect by nicking the sugar-phosphate backbone at this point. The deoxyribose phosphate is removed and cytosine now pairs with the guanine on the intact strand. The repaired strand is now sealed by DNA ligase. (This also explains why uracil is not used in DNA. It would be impossible to distinguish normal uracil from uracil arising from the deamination of cytosine. Uracil is used in RNA because it is less costly to build, and RNA does not have to be made so accurately, being more temporary, and not inherited, except in some viruses.)

The top strand in the left-hand half of figure 1.7 is replicated continuously in the direction in which the fork is opening up, because polymerases synthesise DNA in the 5′ to 3′ direction, but not in the 3′ to 5′ direction. The bottom strand runs 3′ to 5′, left to right. This means that the process of polymerisation has to proceed from left to right on the bottom strand. But the left-hand replication fork is opening up from the

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