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Fundamentals of Molecular Biology

CONTEMPORARY MOLECULAR BIOLOGY is concerned principally with understanding the mechanisms responsible for transmission and expression of the genetic information that ultimately governs cell structure and function. As reviewed in Chapter 1, all cells share a number of basic properties, and this underlying unity of cell biology is particularly apparent at the molecular level. Such unity has allowed scientists to choose simple organisms (such as bacteria) as models for many fundamental experiments, with the expectation that similar molecular mechanisms are operative in organisms as diverse as *E. coli* and humans. Numerous experiments have established the validity of this assumption, and it is now clear that the molecular biology of cells provides a unifying theme to understanding diverse aspects of cell behavior.

Initial advances in molecular biology were made by taking advantage of the rapid growth and readily manipulable genetics of simple bacteria, such as *E. coli*, and their viruses. More recently, not only the fundamental principles but also many of the experimental approaches first developed in prokaryotes have been successfully applied to eukaryotic cells. The development of recombinant DNA has had a tremendous impact, allowing individual eukaryotic genes to be isolated and characterized in detail. Current advances in recombinant DNA technology have made even the determination of the complete sequence of the human genome a feasible project.

HEREDITY, GENES, AND DNA

Perhaps the most fundamental property of all living things is the ability to reproduce. All organisms inherit the genetic information specifying their structure and function from their parents. Likewise, all cells arise from preexisting cells, so the genetic material must be replicated and passed from parent to progeny cell at each cell division. How genetic information is replicated and transmitted from cell to cell and organism to organism thus represents a question that is central to all of biology. Consequently, elucidation of the mechanisms of genetic transmission and identification of the genetic material as DNA were discoveries that formed the foundation our current understanding of biology at the molecular level.

Genes and Chromosomes

The classical principles of genetics were deduced by Gregor Mendel 1865, on the basis of the results of breeding experiments with pea Mendel studied the inheritance of a number of well-defined traits, suc as seed color, and was able to deduce general rules for their transmissio: In all cases, he could correctly interpret the observed patterns of inher tance by assuming that each trait is determined by a pair of inherited fa tors, which are now called **genes**. One gene copy (called an **allele**) spec fying each trait is inherited from each parent. For example, breeding tw strains of peas—one having yellow seeds, and the other green seeds– yields the following results (Figure 3.1). The parental strains each hav two identical copies of the gene specifying yellow (*Y*) or green (*y*) seed: respectively. The progeny plants are therefore hybrids, having inherite one gene for yellow seeds (*Y*) and one for green seeds (*y*). All these prog eny plants (the first filial, or F_1, generation) have yellow seeds, so yellov (*Y*) is said to be **dominant** and green (*y*) **recessive**. The **genotype** (geneti composition) of the F_1 peas is thus *Yy*, and their **phenotype** (physica appearance) is yellow. If one F_1 offspring is bred with another, giving ris to F_2 progeny, the genes for yellow and green seeds segregate in a char acteristic manner such that the ratio between F_2 plants with yellow seed: and those with green seeds is 3:1.

Mendel's findings, apparently ahead of their time, were largely ignored until 1900, when Mendel's laws were rediscovered and their importance recognized. Shortly thereafter, the role of **chromosomes** as the carriers of genes was proposed. It was realized that most cells of higher plants and animals are **diploid**—containing two copies of each chromosome. Formation of the germ cells (the sperm and egg), however, involves a unique type of cell division (**meiosis**) in which only one member of each chromosome

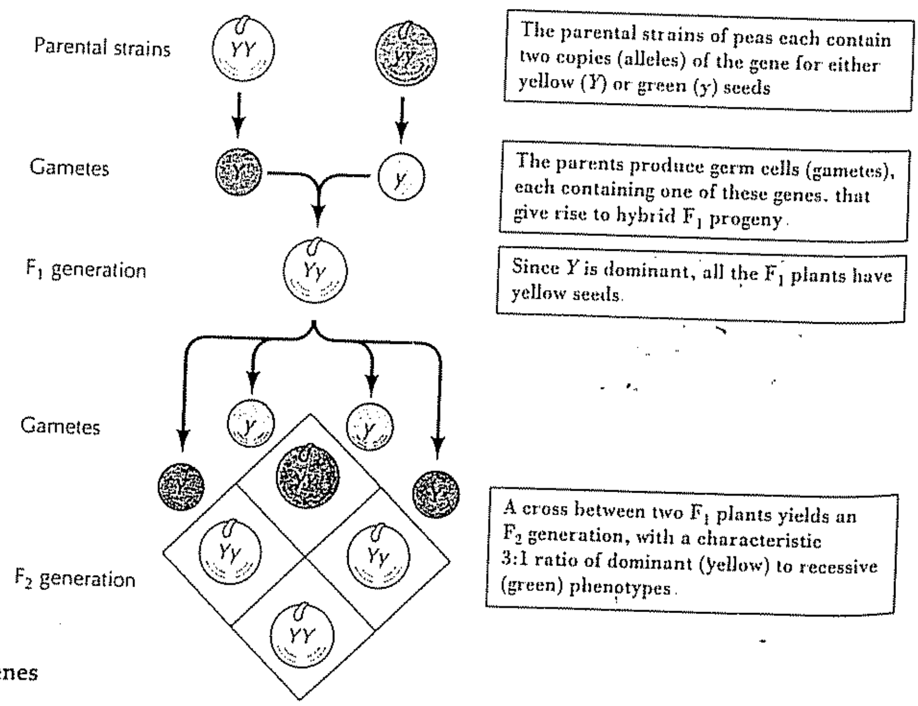

Figure 3.1
Inheritance of dominant and recessive genes

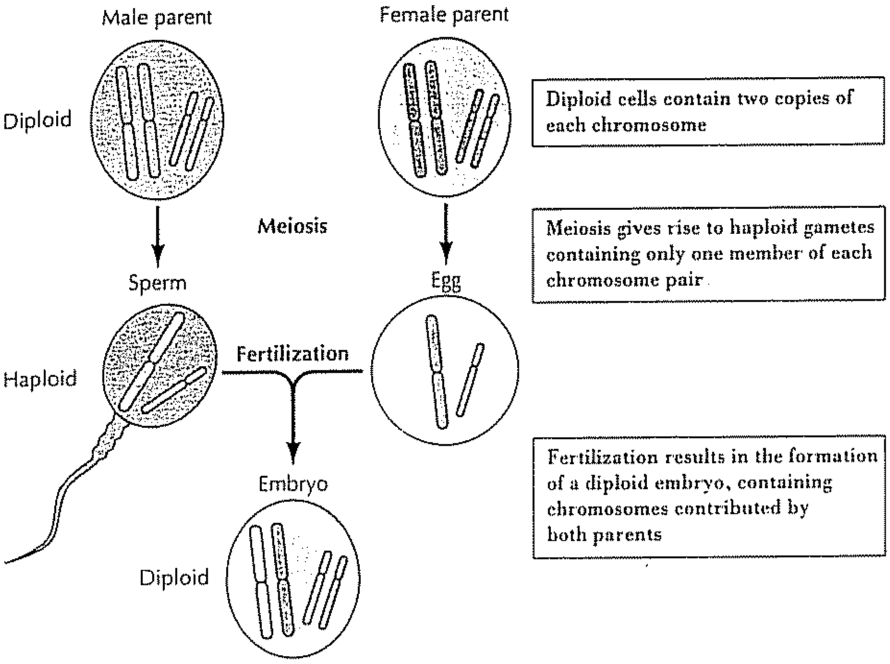

Figure 3.2
Chromosomes at meiosis and fertilization Two chromosome pairs of a hypothetical organism are illustrated

pair is transmitted to each progeny cell (Figure 3.2). Consequently, the sperm and egg are **haploid**, containing only one copy of each chromosome The union of these two haploid cells at fertilization creates a new diploid organism, now containing one member of each chromosome pair derived from the male and one from the female parent. The behavior of chromosome pairs thus parallels that of genes, leading to the conclusion that genes are carried on chromosomes.

The fundamentals of mutation, genetic linkage, and the relationships between genes and chromosomes were largely established by experiments performed with the fruit fly, *Drosophila melanogaster* *Drosophila* can be easily maintained in the laboratory, and they reproduce about every two veeks, which is a considerable advantage for genetic experiments. Indeed, these features continue to make *Drosophila* an organism of choice for genetic studies of animals, particularly the genetic analysis of development and differentiation.

In the early 1900s, a number of genetic alterations (**mutations**) were dentified in *Drosophila*, usually affecting readily observable characteristics such as eye color or wing shape. Breeding experiments indicated that some of the genes governing these traits are inherited independently of each other, suggesting that these genes are located on different chromosomes that segregate independently during meiosis (Figure 3.3). Other genes, however, are frequently inherited together as paired characteristics. Such genes are said to be linked to each other by virtue of being located on the same chromosome. The number of groups of linked genes is the same as the number of chromosomes (four in *Drosophila*), supporting the idea that chromosomes are carriers of the genes.

Linkage between genes is not complete, however; chromosomes exchange material during meiosis, leading to **recombination** between linked genes (Figure 3.4). The frequency of recombination between two linked genes depends on the distance between them on the chromosome; genes that are close to each other recombine less frequently than do genes farther apart. Thus, the frequencies with which different genes recombine can be used to

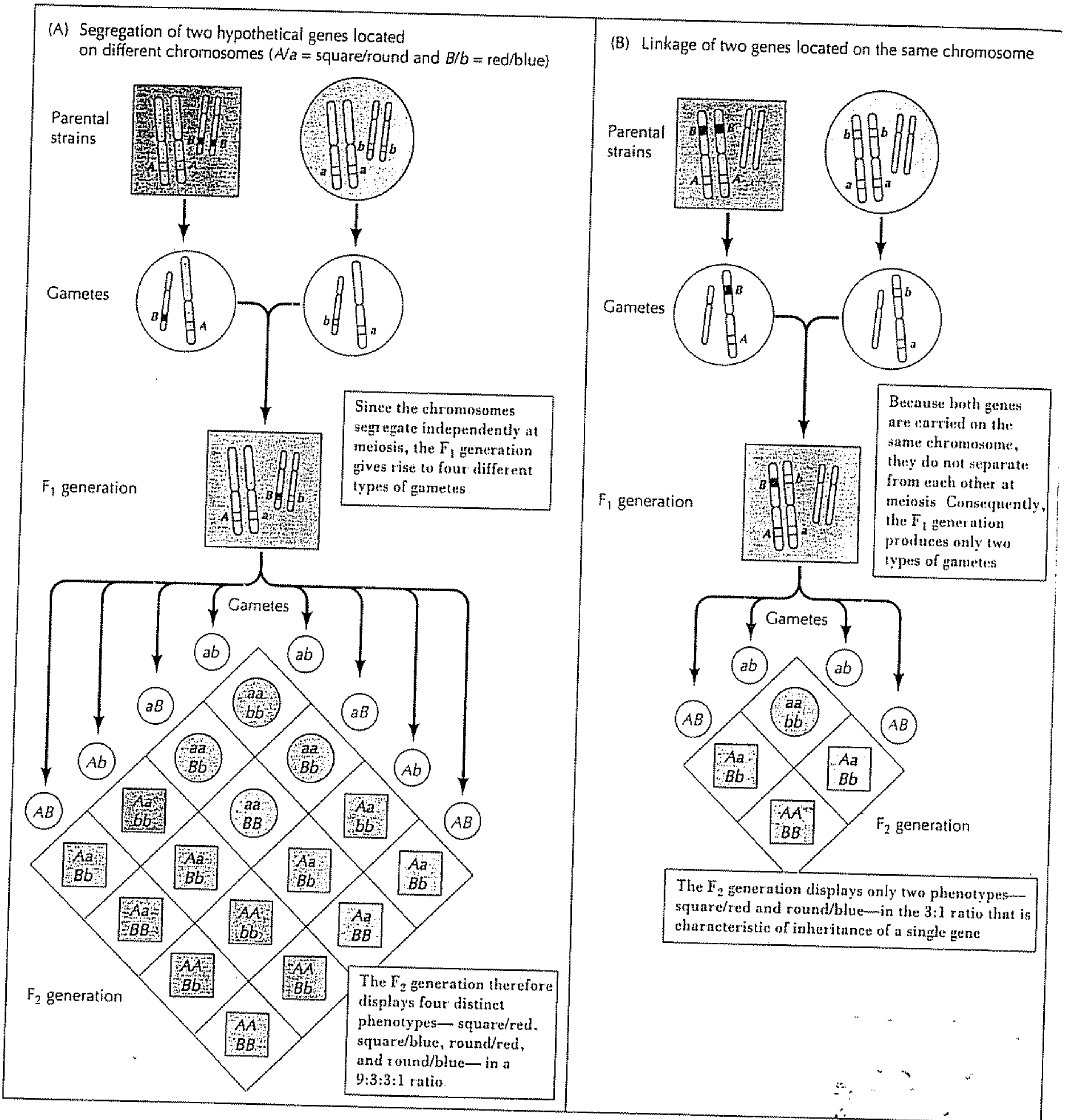

Figure 3.3
Gene segregation and linkage
(A) Segregation of two hypothetical genes for shape (A/a = square/round) and color (B/b = red/blue) located on different chromosomes (B) Linkage of two genes located on the same chromosome.

determine their relative positions on the chromosome, allowing the construction of genetic maps (Figure 3.5). By 1915, nearly a hundred genes had been defined and mapped onto the four chromosomes of *Drosophila*, leading to general acceptance of the chromosomal basis of heredity.

Genes and Enzymes

Early genetic studies focused on the identification and chromosomal localization of genes that control readily observable characteristics, such as the