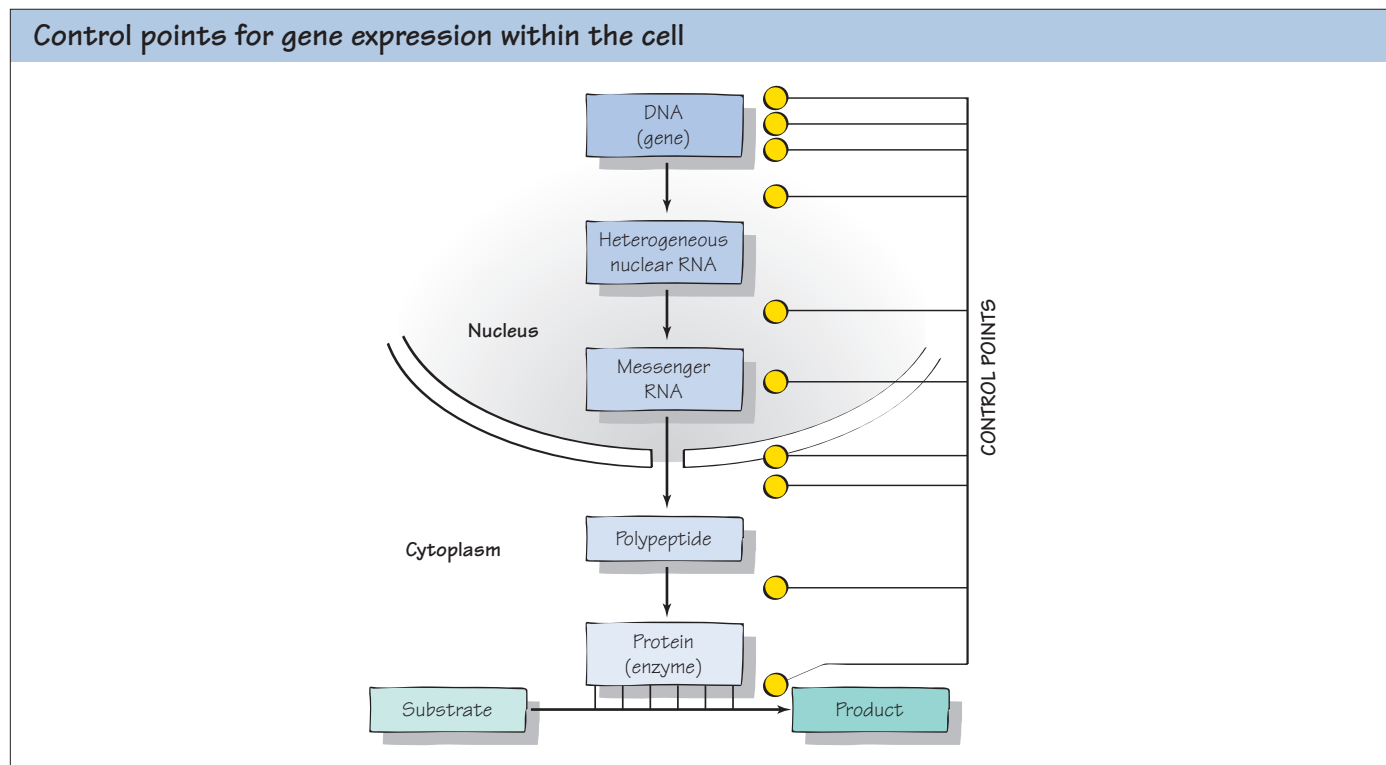


1 Introduction and basic biology



The case for genetics

Medicine is currently in a state of transformation, created by the convergence of two major aspects of technological advance. The first is the explosion in information technology, and the second the rapidly expanding science of genetics. The likely outcome is that within the foreseeable future we will see the introduction of a new kind of medicine, **individualized medicine**, tailored uniquely to the personal needs of each patient.

Clinicians currently use family histories and genetic testing to identify patients for further evaluation and for guidance on their management. Recognition of the precise (molecular) nature of a disorder enables correct interpretation of ambiguous symptoms. Some diseases, such as hypertension (high blood pressure), have many causes for which a variety of treatments may be possible. Identification of precise cause would allow clinicians to give personal guidance on the avoidance of adverse stimuli and enable precise targeting of the disease with personally appropriate medications. Progress along those lines has been slower than anticipated, but has now moved powerfully into related areas.

Pharmacogenetics is the study of differential responses to unusual biochemicals. For genetic reasons some individuals are hypersensitive to standard doses of commonly prescribed drugs, while others respond poorly. Genetic insight will guide physicians in the correct prescription of doses while discoveries in other areas of genetics are stimulating development of new kinds of medication. The field of **pharmacogenomics** involves the genetic engineering of pharmaceuticals. Human genes, such as those for insulin and interferon are introduced into

microorganisms, field crops and farm animals and these species used as living factories for production of the human proteins. Genomics is also leading to the elucidation of molecular pathways of disease and the ability to target specific steps in these pathways.

In research into human diseases, **disease analogues** can be created in laboratory animals by targeted deletion of genes of interest. This approach has been used to create animal models for a wide variety of diseases such as cystic fibrosis and neurofibromatosis.

Some of these topics are outside the scope of this book, but the reader should have no doubt that the medicine of the future, the medicine he or she will practice, will rely very heavily on the insights provided by genetics.

Overview of Part 1

Although medical genetics is essentially about the transmission of harmful versions of genes from one generation to the next, it encompasses a great deal more. Part 1 covers the basic cellular, molecular and developmental biology necessary for its understanding.

The cell (Chapter 2)

Typically every cell in our bodies contains a pair of each of our genes and these are controlled and expressed in molecular terms *at the level of the cell*. During embryonic development cells in different parts of the body become exposed to different influences and acquire divergent properties, as they begin to express different combinations of the 20–25 000 gene pairs they each contain. Nevertheless, most cells have a similar basic structure and composition, as described in Chapter 2.

Genetic material (Chapters 3–5)

Most of the biochemical processes of our bodies are catalysed by enzymes and their amino acid sequences are defined by the genes. Genes are coded messages written into an enormously long molecule called **DNA**. This is elaborately coiled and in growing tissue is found alternately extended or tightly contracted.

The DNA is distributed between 23 pairs of homologous **chromosomes**. In a normal woman two of these are large **X-chromosomes**. A normal man also has 46 chromosomes, but in place of one X is a much smaller **Y**, that carries several genes, including the single gene responsible for triggering male development.

Gene expression (Chapters 6–8)

The means by which the information contained in the DNA is interpreted is so central to our understanding that the phrase: '*DNA makes RNA makes protein*'; or, more correctly, '*DNA makes heterogeneous nuclear RNA, which makes messenger RNA, which makes polypeptide, which makes protein*'; has become accepted as the '**central dogma**' of molecular biology. The production of the protein product of any gene can potentially be controlled at many steps (see figure).

Cell division and formation of eggs and sperm

(Chapters 9 and 10)

Body growth involves individual cells replicating their components, dividing in half, expanding and doing the same again. This sequence is called **the cell cycle** and it involves two critical events: **replication** of chromosomal DNA, and segregation of the duplicated chromosomes by **mitosis**.

A modified version of mitosis results in cells with only one, instead of two, sets of chromosomes. This is **meiosis**, which plays a critical part in the creation of the gametes.

Embryonic development (Chapters 11–13)

Fertilization of an egg by a sperm restores the normal chromosome number in the resultant **zygote**. This proliferates to become a hollow ball that **implants** in the maternal uterus. Development proceeds until birth, normally at around 38 weeks, but all the body organs are present in miniature by 6–8 weeks. Thereafter embryogenesis mainly involves **growth** and **differentiation** of cell types. At **puberty** development of the organs of reproduction is re-stimulated and the individual attains physical maturity. The period of 38 weeks is popularly considered to be 9 months, traditionally interpreted as three '**trimesters**'. The term '**mid-trimester**' refers to the period covering the 4th, 5th and 6th months of gestation.

Genotype and phenotype

Genotype is the word geneticists use for the genetic endowment a person has inherited. **Phenotype** is our word for the anatomical, physiological and psychological complex we recognize as an individual.

People have diverse phenotypes, partly because they inherited different genotypes, but an equally important factor is what we can loosely describe as 'environment'. This includes nutrients derived from the bodies of our mothers, growing space, our postnatal feeding and experience, sunlight, exercise, etc. A valuable concept is summarized in the statement: '*Phenotype is the product of interaction between genotype, environment and time*'; or:

$$\text{Phenotype} = \text{Genotype} \times \text{Environment} \times \text{Time}$$

Practically every aspect of phenotype has both genetic and environmental components. This is a point well worth remembering when we consider the possible causes of any disease, and an issue we address more closely in Part 2.