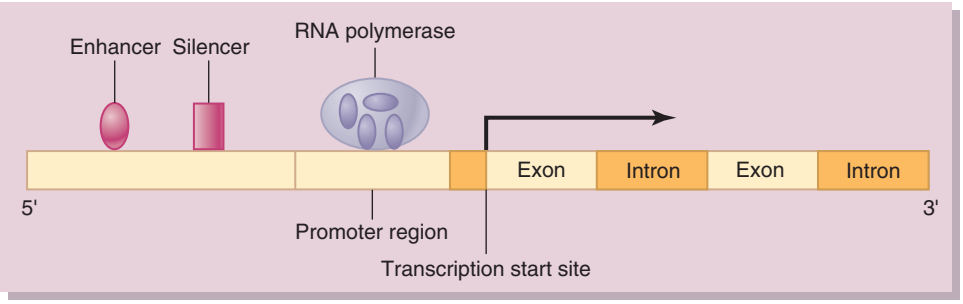

FIGURE 1-1 Transcription. Genomic DNA is shown with enhancer and silencer sites located 5′ upstream of the promoter region, to which RNA polymerase is bound. The transcription start site is shown downstream of the promoter region, and this site is followed by exonic sequences interrupted by intronic sequences. The former sequences are transcribed one after another (ad seriatim) by the RNA polymerase.

residues. All tRNA precursors and other rRNA molecules are synthesized by RNA polymerase III in the nucleoplasm.

RNA polymerases are synthesized from precursor transcripts that must be cleaved into subunits before further processing and assembling with ribosomal proteins into macromolecular complexes. Ribosomal architectural and structural integrity are derived from the secondary and tertiary structures of rRNA, which assume a series of folding patterns containing short duplex regions. Precursors of tRNA in the nucleus undergo the removal of the 5′ leader region, splicing of an internal intron sequences, and modification of terminal residues.

Precursors of mRNA are produced in the nucleus by the action of DNA-dependent RNA polymerase II, which copies the *antisense* strand of the DNA double helix to synthesize a single strand of mRNA that is identical to the *sense* strand of the DNA double helix in a process called *transcription* (Fig. 1-1). The initial, immature mRNA first undergoes modification at the 5′ and 3′ ends. A special nucleotide structure called the *cap* is added to the 5′ end, which increases binding to the ribosome and enhances translational efficiency. The 3′ end undergoes modification by nuclease cleavage of about 20 nucleotides, followed by the addition of a length of polynucleotide sequence containing a uniform stretch of adenine bases, the so-called poly-A tail that stabilizes the mRNA.

In addition to these changes that occur uniformly in all mRNAs, more selective modifications can occur. Because each gene contains exonic and intronic sequences and the precursor mRNA is transcribed without regard for exon-intron boundaries, this immature message must be edited so that all exons are spliced together in an appropriate sequence. The process of splicing, or removing intronic sequences to produce the mature mRNA, is an exquisitely choreographed event that involves the intermediate formation of a spliceosome, which is a large complex consisting of small nuclear RNAs and specific proteins that contains a loop or lariat-like structure that includes the intron targeted for removal. Only after splicing, a catalytic process requiring adenosine triphosphate hydrolysis, has concluded is the mature mRNA able to transit from the nucleus into the cytoplasm, where the encoded information is translated into protein.

Alternative splicing is a process for efficiently generating multiple gene products that often are dictated by tissue specificity, developmental expression, and pathologic state. Gene splicing allows the expression of multiple isoforms by expanding the repertoire for molecular diversity. An estimated 30% of genetic

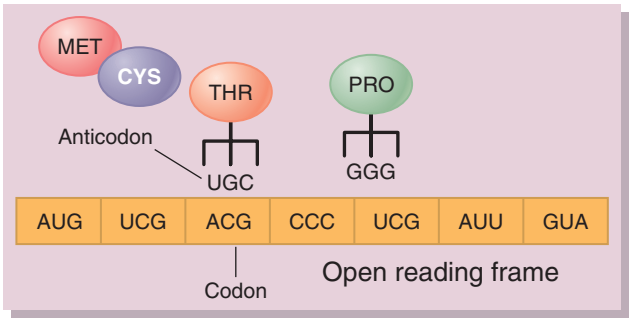

FIGURE 1-2 Translation. The open reading frame of a mature messenger RNA is shown with its series of codons. Transfer RNA molecules are shown with their corresponding anticodons, charged with their specific amino acid. A short, growing polypeptide chain is depicted. A, Adenine; C, cytosine; CYS, cysteine; G, guanine; MET, methionine; PRO, proline; THR, threonine; U, uracil.

diseases in humans arise from defects in splicing. The resulting mature mRNA then exits the nucleus to begin the process of *translation* or conversion of the base code to polypeptide (Fig. 1-2). Alternative splicing pathways (i.e., alternative exonic assembly pathways) for specific genes also serve at the level of transcriptional regulation. The discovery of catalytic RNA, which enables self-directed internal excision and repair, has advanced the view that RNA serves as a template for translation of the genetic code and simultaneously as an enzyme (see Transcriptional Regulation).

Protein synthesis, or translation of the mRNA code, occurs on ribosomes, which are macromolecular complexes of proteins and rRNA located in the cytoplasm. Translation involves the conversion of the linear code of a triplet of bases (i.e., codon) into the corresponding amino acid. A four-base code generates 64 possible triplet combinations ($4 \times 4 \times 4$), and they correspond to 20 different amino acids, many of which are encoded by more than one base triplet. To decode mRNA, an adapter molecule (tRNA) recognizes the codon in mRNA through complementary base pairing with a three-base anticodon that it bears; each tRNA is charged with a unique amino acid that corresponds to the anticodon (Fig. 1-3).

Translation on the mRNA template proceeds without punctuation of the non-overlapping code with the aid of rRNA on an assembly machine called a *ribosome*—essentially a polypeptide polymerase. At least one tRNA molecule exists for each of the 20 amino acids, although degeneracy in the code expands the