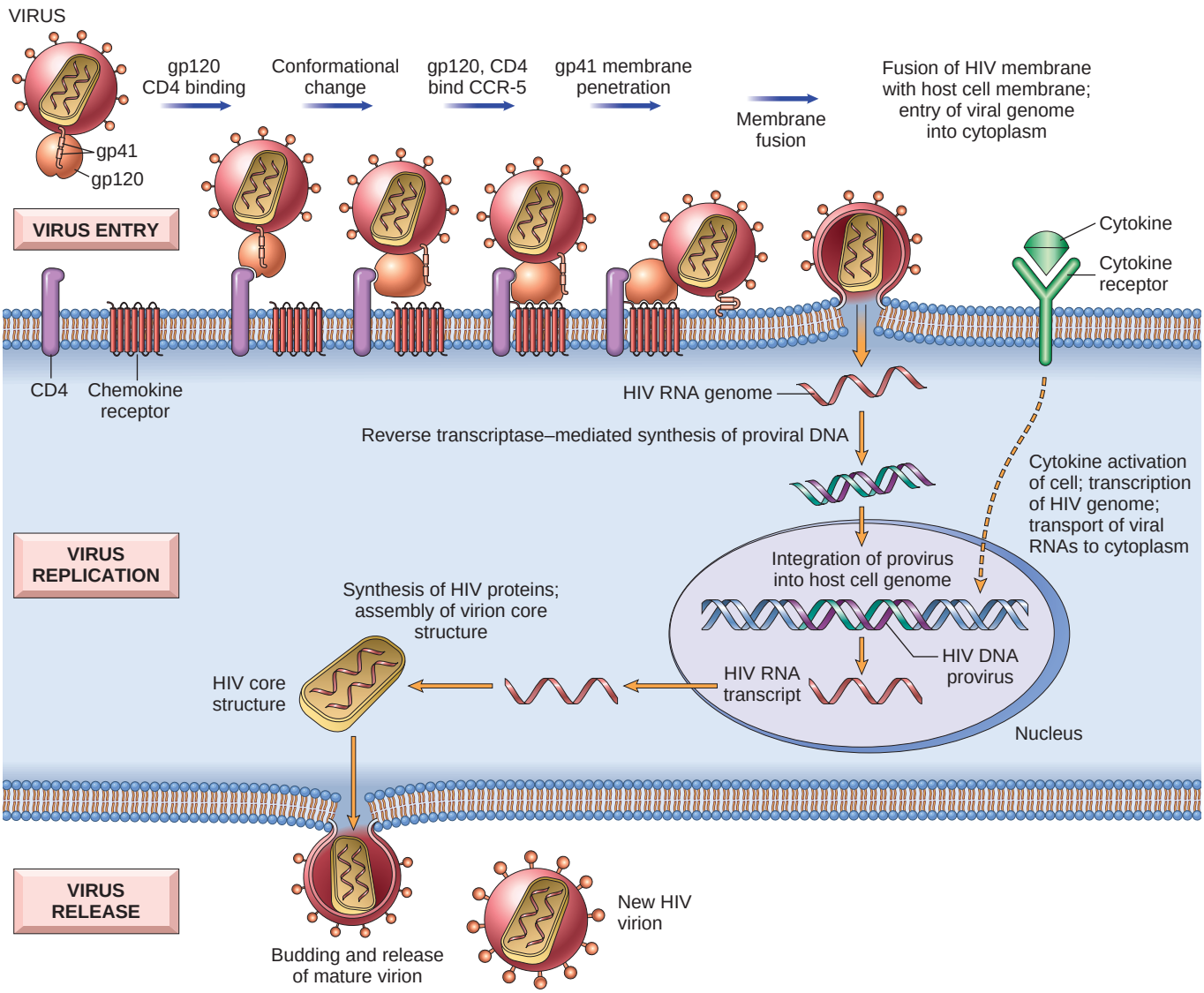

Figure 6-40 The life cycle of HIV showing the steps from viral entry to production of infectious virions. (Adapted with permission from Wain-Hobson S: HIV. One on one meets two. Nature 1996;384:117. Copyright 1996, Macmillan Magazines Limited.)

a conformational change that results in the formation of a new recognition site on gp120 for the coreceptors CCR5 or CXCR4. Binding to the coreceptors induces conformational changes in gp41 that result in the exposure of a hydrophobic region called the fusion peptide at the tip of gp41. This peptide inserts into the cell membrane of the target cells (e.g., T cells or macrophages), leading to fusion of the virus with the host cell. After fusion the virus core containing the HIV genome enters the cytoplasm of the cell. The requirement for HIV binding to coreceptors may have important implications for the pathogenesis of AIDS. Chemokines sterically hinder HIV infection of cells in culture by occupying their receptors, and therefore, the level of chemokines in the tissues may influence the efficiency of viral infection in vivo. Also, polymorphisms in the gene encoding CCR5 are associated with different susceptibility to HIV infection. About 1% of white Americans inherit two defective copies of the CCR5 gene and are resistant to infection and the development of AIDS associated with R5 HIV isolates. About 20% of individuals are heterozygous for this protective CCR5 allele; these persons are not protected from AIDS, but the onset of their disease after infection is somewhat delayed. Only rare homozygotes for the mutation have been found in African or East Asian populations.

Viral Replication

Once internalized, the RNA genome of the virus undergoes reverse transcription, leading to the synthesis of double-stranded complementary DNA (cDNA; proviral DNA) (Fig. 6-40). In quiescent T cells, HIV cDNA may remain in the cytoplasm in a linear episomal form. In dividing T cells, the cDNA circularizes, enters the nucleus, and is then integrated into the host genome. After this integration, the provirus may be silent for months or years, a form of latent infection. Alternatively, proviral DNA may be transcribed, with the formation of complete viral particles that bud from the cell membrane. Such productive infection, when associated with extensive viral budding, leads to death of infected cells.