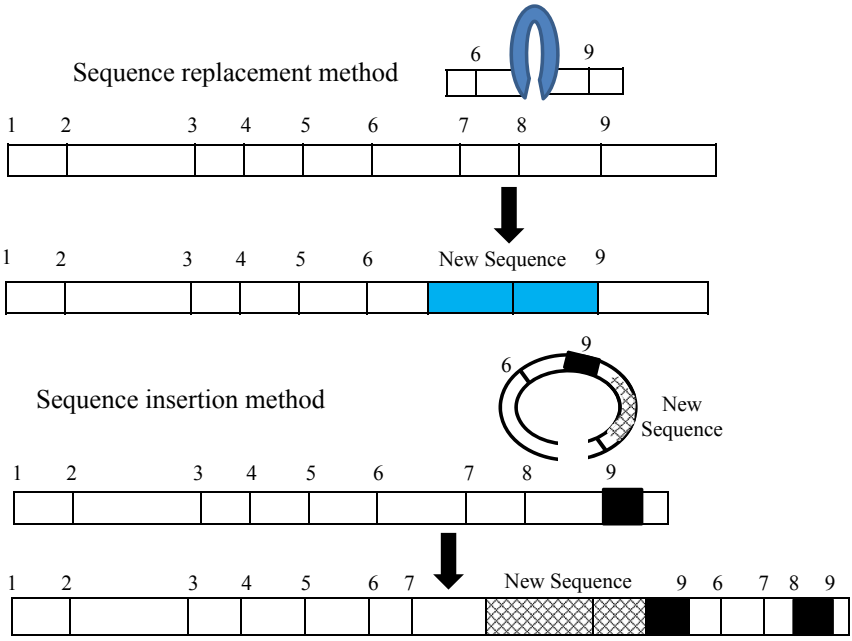

FIGURE 2.11 In the sequence replacement method of producing knockout animal models, gene disruption is accomplished by replacing a portion of the target DNA with a new sequence. An alternative method of producing knockout animals, the sequence insertion method, inserts a new sequence of DNA that is a repeat of a portion of the original DNA sequence. In both instances, the DNA is no longer capable of producing the gene product. Genetic screening of offspring animals followed by selective breeding can then be used to establish the germ line.

from hypercholsteroemia.[40] Since the introduction of knockout technology, thousands of knockout mice have been created in an effort to better understand gene function and disease progression. The importance of this technology was recognized in 2007 with the awarding of the Nobel Prize to Capecchi, Evans, and Smithies for their pioneering work in this area.[41]

Milestones in Molecular Science

While advances in animal models were providing more and more information into the physiological outcomes of potential therapies, they provided little, if any, knowledge as to the molecular interaction required for biological activity. Elucidating the mechanistic aspects of drug action or disease progression at a molecular level requires the ability to prepare molecules suitable for testing, an understanding of the structure of the target (e.g., enzymes, receptors, etc. See Chapter 3), and the ability to screen for biological activity in isolated systems (e.g., *in vitro* screening. See Chapter 4). In the intervening time between Paul Ehrlich's pioneering