3.5 ALLOSTERIC INHIBITION OF RIBONUCLEOTIDE REDUCTASE VIA INHIBITION OF PURINE NUCLEOSIDE PHOSPHORYLASE

Therapeutically significant inhibition of RNR can also be achieved through a feedback mechanism by accumulation of deoxyguanosine triphosphate (dGTP) as a consequence of the inhibition of purine nucleoside phosphorylase (PNP), an enzyme that has a key role in purine catabolism, known as the "salvage pathway." This enzyme, also known as PNPase, catalyzes the phosphorolysis of the N-ribosidic bonds of purine nucleosides and deoxynucleosides to form purine and α-D-phosphorylated ribosyl products. This inhibition leads to increased blood levels of one of its substrates, deoxyguanosine (dG), which is specifically transported and phosphorylated by T-cell deoxynucleoside kinases. This process leads to pathologically elevated levels of dGTP in these cells, which results in allosteric RNR inhibition that results in apoptosis of T lymphocytes and B lymphocytes (Figure 2.13). PNP is

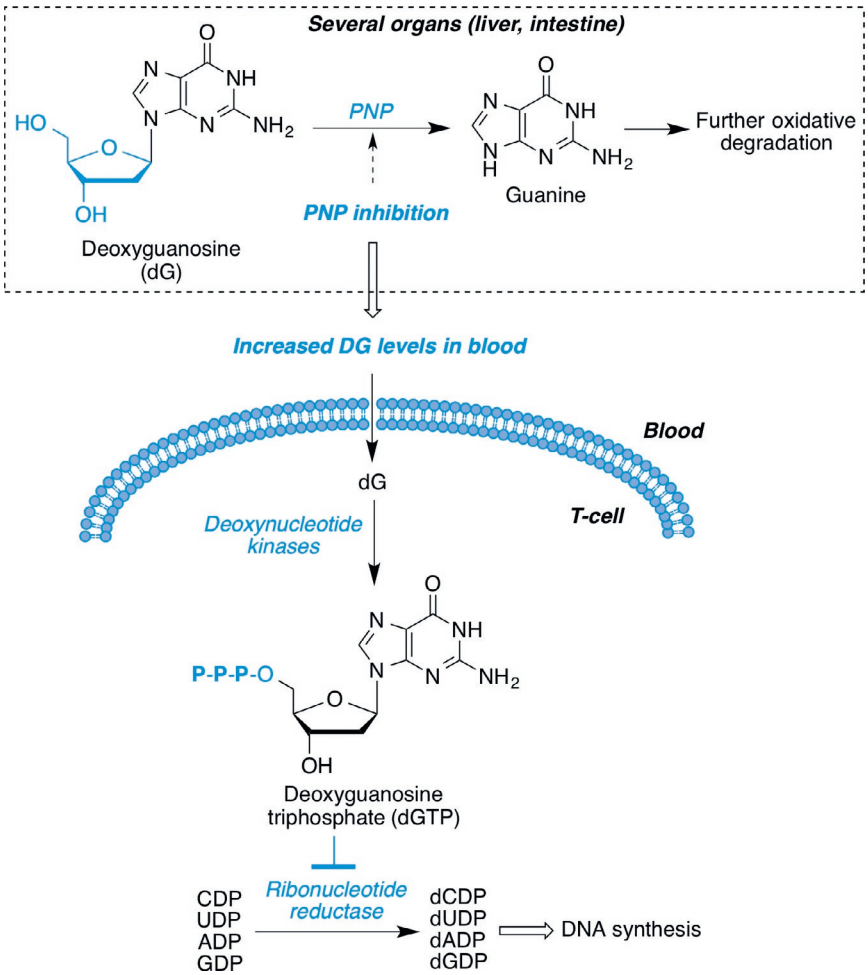

FIGURE 2.13

Feedback inhibition of ribonucleotide reductase.