The first compounds that were studied in clinical trials as hypoxic radiosensitizers were nitroimidazoles. The mechanism of hypoxic-cell sensitizing by the nitro derivatives is based on their ability to react with biomolecule radicals giving a radical adduct that cannot be repaired, thereby acting as oxygen surrogates (Figure 4.49a). Alternatively, addition of the biomolecule radical to the nitro group gives nitro radical anions (Figure 4.49b).

Nitro radical anions are cytotoxic in themselves in hypoxic environments, although normally only at doses too high to be achieved in clinical situations. However, this cytotoxicity is reinforced by the generation of other radical species, some of which are shown in Figure 4.50. It is interesting to mention in this context that the antibacterial and antiprotozoal activity of many nitroheterocycles is explained by one-electron reduction of the nitro group to nitro radical anions.

The first nitro compounds to be clinically studied as radiosensitizers, in the early 1970s, were metronidazole and especially misonidazole, which were studied in a large number of clinical assays.

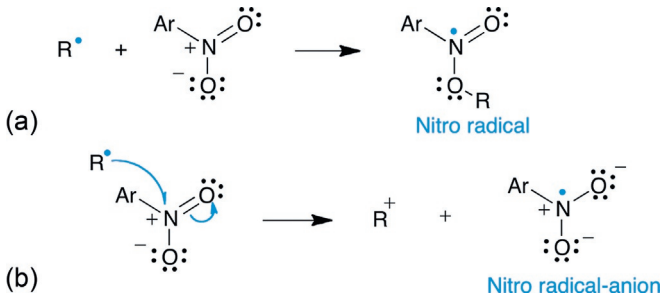

FIGURE 4.49

Generation of nitro radicals (a) and nitro radical anions (b).

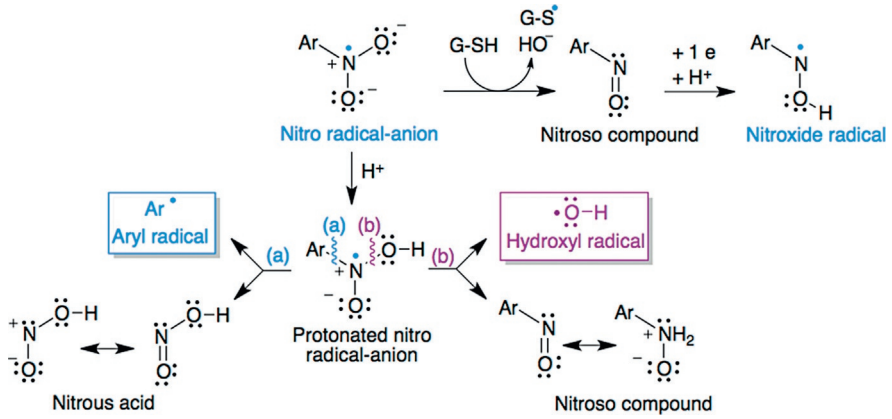

FIGURE 4.50

Cytotoxic radical species generated from nitro radical anions.