detected after incubation of the prodrug in the homogenate of tissue and contents of the small intestine. However, when the dextran prodrug with a DS of 7 or 17 was incubated in rat cecal contents at 37°C, 41 or 32% of the nalidixic acid, respectively, was released within 24 h.

Several amino acids, including phenylalanine, glycine, and leucine, as well as the dipeptide, glycylglycine, and the dicarboxylic acid, succinic acid, were each employed as a spacer to link metronidazole with the dextran backbone (Vermeersch et al., 1990) to prepare water-soluble ester prodrugs with *in vitro* stability and *in vivo* antitrichomonal activity. Succinic or glutaric acid spacers were employed to link methylprednisolone or dexamethasone to dextran for potential colon-specific delivery (McLeod et al., 1993). Little drug was released during incubation with small intestine contents, but faster release rates were observed with cecum and colon contents. Slow hydrolysis rates in pH 6.8 phosphate buffer at 37°C, along with the observed selective enzyme-mediated hydrolysis, and the long residence time in the human colon indicate that these prodrugs indeed have the potential for successful targeted delivery of these glucocorticoids.

A polymeric prodrug was prepared by appending 5-iodo-2′-deoxyuridine (IDU) to poly(*d, l*-lactic acid) (PLA) using succinic acid as a linker (Rimoli et al., 1999). The IDU loading was consistent with the carboxylic acid endgroups (about 0.024 mEq/g of PLA). The conjugate was chemically stable toward hydrolysis in pH 7.4 phosphate buffer, but was susceptible to enzymatic degradation in biological media containing esterases.

Cyclodextrin has shown promise as a polymeric promoiety. A 5-aminosalicylic acid (5-ASA) prodrug was prepared (Zou et al., 2005) by refluxing 5-ASA and formic acid for 30 min, followed by addition of cold distilled water, to generate 5-formylaminosalicylic acid (5-fASA). 5-fASA was then dissolved in DMF and carbonyldiimidazole was added. α-, β-, or γ-cyclodextrin, dissolved in DMSO, was slowly added, and then triethylamine was added. The mixture was stirred for 24 h, and then an excess of HCl or acetone was used to precipitate the 5-formyl version of the prodrug. 5-ASA-appended cyclodextrin prodrug was prepared from the precipitate by hydrolysis of the formyl group. Chemical stability at pH 1.2, 6.8, and 7.5 at 37°C for 6 h was demonstrated for prodrugs with the ratio of cyclodextrin to 5-ASA up to 1:10. Prodrugs with 1:1 or 1:2 ratios provided substantially higher solubility in 25°C, 0.05 M acetic acid solution (91.8–720 g/L) in comparison to that of 5-ASA itself (1.0 g/L), but this low degree of drug loading would result in a high mass to properly dose the patient. After incubation of the prodrugs with the contents of various regions of the gastrointestinal tract of rats, 5-ASA was liberated slowly in the small intestine, with more rapid release in cecal or colonic mixtures, as desired.

Since hyaluronic acid (HA) receptors are overexpressed in transformed human breast epithelial cells and other cancers (Culty et al., 1992), selectivity for cancer cells can be enhanced by appending antitumor agents to HA. In addition to improving the solubility in water, coupling these drugs to biopolymers in general has provided advantages in terms of chemical stability, localization, and controlled release (Maeda et al., 1992). HA is a linear polysaccharide with alternating glucuronic acid and *N*-acetyl-glucosamine residues (Figure 16.5). It is one of the glycosaminoglycan components of the extracellular matrix, the synovial fluid in joints, and the scaffold that comprises cartilage

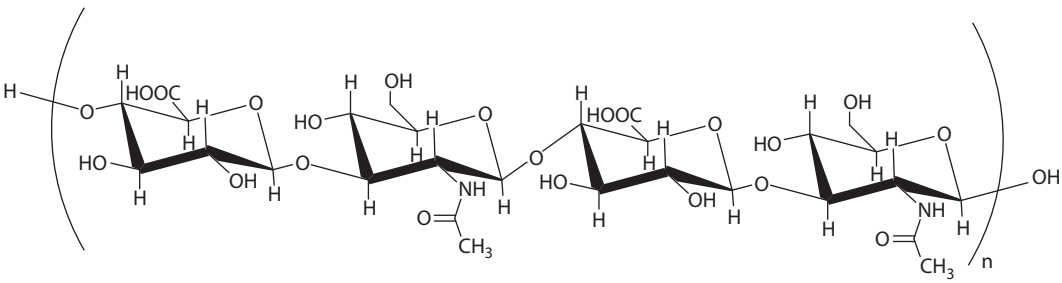

FIGURE 16.5 Hyaluronic acid.