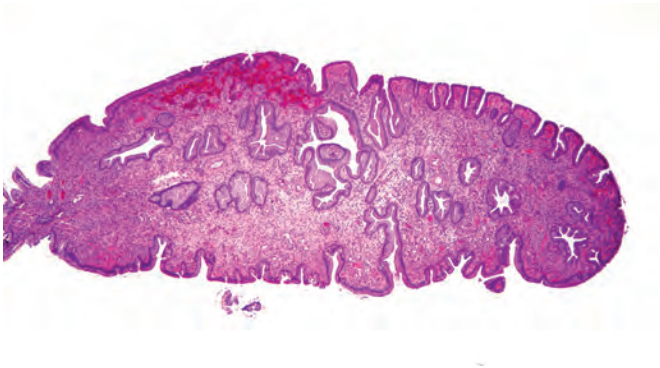

Figure 22-13 Endocervical polyp composed of a dense fibrous stroma covered with endocervical columnar epithelium.

intercourse, or vaginal douching, H_2O_2 production by lactobacilli decreases. Antibiotic therapy that suppress lactobacilli can also cause the pH to rise. In each of these settings the altered vaginal environment promotes the overgrowth of other microorganisms, which may result in cervicitis or vaginitis. Some degree of cervical inflammation may be found in virtually all women, and it is usually of little clinical consequence. However, *infections by gonococci, chlamydiae, mycoplasmas, and HSV may produce significant acute or chronic cervicitis* and are important to identify due to their association with upper genital tract disease, complications during pregnancy, and sexual transmission. Marked cervical inflammation produces reparative and reactive changes of the epithelium and shedding of atypical-appearing squamous cells, and therefore may cause an abnormal Pap test result.

Endocervical Polyps

Endocervical polyps are common benign exophytic growths that arise within the endocervical canal. They vary from small, sessile "bumps" to large polypoid masses that may protrude through the cervical os. Histologically, they are composed of a loose fibromyxomatous stroma covered by mucus-secreting endocervical glands, often accompanied by inflammation (Fig. 22-13). Their main significance is that they may be the source of irregular vaginal "spotting" or bleeding that arouses suspicion of some more ominous lesion. Simple curettage or surgical excision is curative.

Premalignant and Malignant Neoplasms of the Cervix

Worldwide, cervical carcinoma is the third most common cancer in women, with an estimated 530,000 new cases in 2008, of which more than half are fatal. In the United States, 12,410 women were diagnosed with cervical cancer and 4000 women died of the disease in 2008. Fifty years ago, carcinoma of the cervix was the leading cause of cancer deaths in women in the United States, but the death rate has declined by two thirds to its present rank as the thirteenth cause of cancer mortality. No form of cancer better documents the remarkable benefits of effective screening, early diagnosis, and curative therapy than does cancer of the cervix. Much credit for these dramatic gains belongs to the effectiveness of the Pap test in detecting cervical precursor lesions, some of which would have progressed to cancer if not treated; in addition, the Pap test can also detect low-stage, highly curable cancers. The accessibility of the cervix to Pap testing and visual exam (colposcopy) as well as the slow progression from precursor lesions to invasive carcinoma (typically over the course of years) provides ample time for screening, detection, and preventive treatment.

Pathogenesis. **High-risk HPVs are by far the most important factor in the development of cervical cancer**. HPVs are DNA viruses that are typed based on their DNA sequence and grouped into those of high and low oncogenic risk. There are 15 high risk HPVs that are currently identified, but HPV-16 alone accounts for almost 60% of cervical cancer cases, and HPV-18 accounts for another 10% of cases; other HPV types contribute to less than 5% of cases, individually. *High risk HPVs are also implicated in squamous cell carcinomas arising at many other sites, including the vagina, vulva, penis, anus, tonsil, and other oropharyngeal locations* (Chapter 16). As noted earlier, low oncogenic risk HPVs are the cause of the sexually transmitted vulvar, perineal, and perianal warts (condyloma acuminatum).

Genital HPV infections are extremely common; most of them are asymptomatic, do not cause any tissue changes, and therefore are not detected on Pap test. The prevalence of HPV in cervical smears in women with normal Pap test results peaks between the ages of 20 and 24 years, a relationship that is related to the onset of sexual activity, while the subsequent decrease in prevalence reflects acquisition of immunity and entry into monogamous relationships with age. Most HPV infections are transient and are eliminated by the immune response in the course of months. *On average, 50% of HPV infections are cleared within 8 months, and 90% of infections are cleared within 2 years.* The duration of the infection is related to HPV type; on average, infections with high-risk HPVs last longer than infections with low oncogenic risk HPVs (13 months versus 8 months, respectively). Persistent infection increases the risk of the development of cervical precursor lesions and subsequent carcinoma.

HPVs infect immature basal cells of the squamous epithelium in areas of epithelial breaks, or immature metaplastic squamous cells present at the squamocolumnar junction (Fig. 22-11). HPVs cannot infect the mature superficial squamous cells that cover the ectocervix, vagina, or vulva. Establishment of HPV infection in these sites requires damage to the surface epithelium, which allows the virus access to the immature cells in the basal layer of the epithelium. The cervix, with its relatively large areas of immature squamous metaplastic epithelium, is particularly vulnerable to HPV infection as compared to, for example, vulvar skin and mucosa that are covered by mature squamous cells. This difference in epithelial susceptibility to HPV infection accounts for the wide range in incidence of HPV-related cancers arising in various sites, and explains the high frequency of cervical cancer in women and anal cancer in homosexual men and a relatively low frequency of vulvar and penile cancer.

The ability of HPV to act as a carcinogen depends on the viral proteins E6 and E7, which interfere with the activity of tumor suppressor proteins that regulate cell growth and survival. Although HPV infects immature