those associated with cancer. Sections taken from a healing fracture can mimic an osteosarcoma. Moreover, the laboratory evaluation of a lesion can be only as good as the specimen made available for examination. It must be adequate, representative, and properly preserved. Several sampling approaches are available: (1) excision or biopsy, (2) needle aspiration, and (3) cytologic smears. When excision of a small lesion is not possible, selection of an appropriate site for biopsy of a large mass requires awareness that the periphery may not be representative and the center largely necrotic. Appropriate preservation involves such actions as prompt immersion of at least a portion of the specimen in a fixative (usually a formalin solution) and (depending on the differential diagnosis) rapid allocation of tissue for other studies such as cytogenetics, flow cytometry, and molecular diagnostics (described later). Requesting "quick-frozen section" diagnosis is sometimes desirable, for example, in determining the nature of a mass lesion, in evaluating the margins of an excised cancer to ascertain that the entire neoplasm has been removed, or in making decisions about what additional studies beyond histology are needed. This method permits histologic evaluation within minutes. In experienced, competent hands, frozen-section diagnosis is highly accurate, but there are particular instances in which the better histologic detail provided by the more time-consuming routine methods is needed—for example, when extremely radical surgery, such as the amputation of an extremity, may be indicated. Better to wait a day or two, despite the delay, than to perform inadequate or unnecessary surgery.

Fine-needle aspiration of tumors is another approach that is widely used. The procedure involves aspirating cells and attendant fluid with a small-bore needle, followed by cytologic examination of the stained smear. This method is used most commonly for the assessment of readily palpable lesions in sites such as the breast, thyroid, and lymph nodes. Modern imaging techniques permit extension of the method to lesions in deep-seated structures, such as pelvic lymph nodes and pancreas. Fine-needle aspiration is less invasive and more rapidly performed than are needle biopsies. It obviates surgery and its attendant risks. Although it entails some difficulties, such as small sample size and sampling errors, in experienced hands it is reliable, rapid, and useful.

Cytologic smears provide yet another method for the detection of cancer (Chapter 22). This approach is widely used to screen for carcinoma of the cervix, often at an in situ stage, but it is also used to evaluate many other forms of suspected malignancy in which tumor cells are easily accessible or shed, such as endometrial carcinoma, lung carcinoma, bladder and prostatic tumors, and gastric carcinomas; for the identification of tumor cells in abdominal, pleural, joint, and cerebrospinal fluids; and, less commonly, with other forms of neoplasia.

As pointed out earlier, cancer cells have lowered cohesiveness and exhibit a range of morphologic changes encompassed by the term anaplasia. Thus, shed cells can be evaluated for the features of anaplasia indicative of their origin from a tumor (Figs. 7-47 and 7-48). In these cases, judgment must be rendered based on the features of individual cells or, at most, a clump of cells, without the supporting evidence of loss of orientation of one cell to another, and (most importantly) evidence of invasion. This

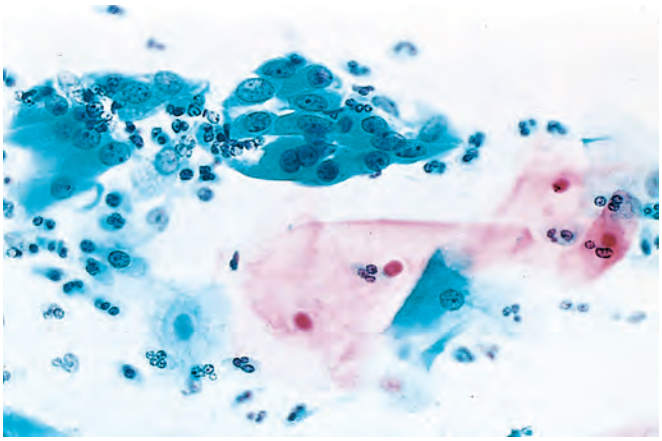

Figure 7-47 A normal cervicovaginal smear shows large, flattened squamous cells and groups of metaplastic cells; interspersed are neutrophils. There are no malignant cells. (Courtesy Dr. P. K. Gupta, University of Pennsylvania, Philadelphia, Pa.)

method permits differentiation among normal, dysplastic, and malignant cells and, in addition, permits the recognition of cellular changes characteristic of carcinoma in situ. The gratifying control of cervical cancer through screening with Pap smears is the best testament to the value of cytology.

Although histology and exfoliative cytology remain the foundation of cancer diagnosis, they have inherent limits; for example, it can be difficult to determine the nature of a poorly differentiated tumor of any type, and some specific tumor types are notoriously difficult to distinguish based on their morphologic appearance alone (e.g., various types of acute leukemias and lymphomas). These limitations have spurred the widespread application of immunohistochemistry and flow cytometry, which can be used to make these diagnostic distinctions. Another rapidly expanding modality is molecular diagnostics, which is being used increasingly to identify cancers that are amenable to treatment with so-called targeted therapies, drugs that are directed at mutated oncoproteins. Only some highlights of these diagnostic modalities are presented.

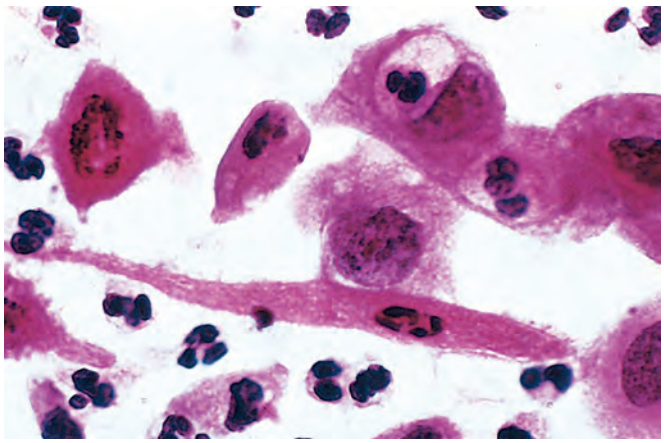

Figure 7-48 An abnormal cervicovaginal smear shows numerous malignant cells that have pleomorphic, hyperchromatic nuclei; interspersed are normal polymorphonuclear leukocytes. (Courtesy Dr. P. K. Gupta, University of Pennsylvania, Philadelphia, Pa.)