Chapter 3
Pancreatic Intraepithelial Neoplasia

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1 Introduction

Most pancreatic cancers are not diagnosed until after the cancer has spread to other organs and is no longer curable. As a result, the death rate for pancreatic cancer in this country (34,290/year) is approximately equal to the incidence rate (37,680/year) (1). By contrast, many patients survive the diagnosis of breast cancer, and half of the decline in breast cancer mortality in the last quarter of a century has come from improved early detection (2). We believe that early detection of preinvasive lesions is the greatest hope for curing pancreatic neoplasia. This chapter discusses pancreatic intraepithelial neoplasia (PanIN), the most common precursor lesion in the pancreas (3).

2 Morphology of PanINs

Although the PanIN nomenclature is a relatively recent development, the lesions now recognized as PanINs were, in fact, described over 100 years ago (4). In 1905 the Dutch physician von S.P.L. Hulst described lesions characterized by enlargement of the cells as well as the architectural formation of papillae (“Hypertrophie der Zellen . . . relative reine päpilare Wucherung”) with a morphologic appearance between that of normal pancreatic ducts and invasive cancer (“Zwischenformen”) (4). These lesions are now called pancreatic intraepithelial neoplasia, recognizing that they are noninvasive intraepithelial neoplasms (5, 6). PanINs are defined as microscopic papillary or flat, noninvasive intraepithelial neoplasms arising in the smaller pancreatic ducts (6). PanIN lesions have been classified into three grades, one of which is subdivided into A and B subcategories (5–7). PanIN-1A is a flat epithelial lesion composed of columnar cells, with basally located uniform round to oval uniform nuclei (Fig. 3.1) (5–7). The cells can contain abundant mucin and the nuclei are well oriented relative to the basement membrane. Molecular analyses suggest that many lesions with this morphology are neoplastic, some may be non-neoplastic, and the addition of the modifier “L” for lesion (PanIN-1A/L) is therefore
perfectly acceptable (5–7). PanIN-1B is papillary, but is otherwise morphologically identical to PanIN-1A (5–7). Most PanIN-2 lesions are papillary, and PanIN-2 lesions, by definition, have some nuclear abnormalities, including some loss of polarity, nuclear crowding, enlarged nuclei, pseudostratification, and hyperchromasia (see Fig. 3.1) (5–7). Mitoses are rare in PanIN-2 lesions, and when present are basal and morphologically normal (5–7). PanIN-3 lesions show significant architectural and cytological atypia (see Fig. 3.1) (5–7). PanIN-3 lesions can show cribriforming, the budding off of clusters of cells, and luminal necrosis (5–7). Cytologically the nuclei are enlarged, hyperchromatic and show a loss of orientation such that they are no longer oriented perpendicular to the basement membrane, and the nuclear to cytoplasmic ratio is increased (5–8). Nucleoli are prominent, and mitoses may be luminal or atypical (5–7).

Recently, Brune et al. and Detlefsen et al. have described distinctive changes in the pancreatic parenchyma that are often associated with PanIN lesions (9, 10). The normal pancreatic parenchyma is free of inflammation and scarring, and is composed of lobules of uniform acinar cells surrounding a central duct. The acinar cells have abundant apical cytoplasm and form barely perceptible lumina (10). Some PanIN lesions are associated with atrophic changes in this acinar parenchyma (Fig. 3.2) (9,