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Prostatic Intraepithelial Neoplasia: a Potential Precursor Lesion of Prostatic Adenocarcinoma

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The necessity of early detection of prostate cancer renewed interest regarding putative premalignant lesions in the tumorigenesis of the prostate. Prostatic intraepithelial neoplasia (PIN) is one potential precursor for prostatic adenocarcinoma. The term PIN has been adopted to replace a wide range of synonyms in the literature that describe potential precursors. PIN is an intraluminal proliferation of the secretory cells lining architecturally benign prostatic ducts and acini that exhibit cytologic atypia. In this review, we discuss the histologic features, the differential diagnosis, the evidence that PIN is a precursor of prostatic carcinoma, and the clinical significance of PIN.

Key Words: Prostate carcinoma, PIN, putative precursor

Prostate cancer is the most commonly diagnosed cancer in men and the second leading cause of death from cancer in men in the United States (Boring *et al.* 1993). Control of prostate cancer represents a serious public health problem, which may intensify as the proportion of elderly men increases in the United States' population (Littrup *et al.* 1993). A multidisciplinary approach using digital rectal examination, transrectal ultrasound, and prostate-specific antigen (PSA) assay has been adopted for the early detection of prostate cancer. However, despite these efforts, 33% of patients still have advanced cancer at the time of diagnosis (Mettlin *et al.* 1993). If definite precursor lesions to prostate cancer are morphologically identified, an early detection for invasive carcinoma could be facilitated. The concept of tumor development through a multistep process via premalignant lesions has been well established in a number of organs, including the uterine cervix, the endometrium, the gastrointestinal tract, the urothelium, and the respiratory epithelium and, in these organs premalignant lesions have been well recognized (Del Regato and Ackerman 1985; Schade and Swinney 1968). Since the first description of premalignant change in the prostate (Oerteil 1926), a number of reports have appeared in the literature describing these lesions with a wide range of synonyms (i.e., atypical glandular hyperplasia, intraductal dysplasia, intraglandular dysplasia, large acinar atypical hyperplasia, atypical epithelial hyperplasia, and cytologic atypia). The term prostatic intraepithelial hyperplasia (PIN) was endorsed by consensus at a 1989 international conference to replace these various synonyms used in the literature (Drago *et al.* 1989). In this review, we discuss four important points regarding PIN: histologic features with grading, differential diagnoses, evidences as a precursor lesion, and clinical signficance.

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HISTOLOGIC FEATURES

PIN is a process involving both prostatic ducts

and acini. It is characterized by proliferation of secretory cells within the pre-existing ducts and acini, accompanied by cytologic atypia. Features of PIN include cellular crowding and stratification, variation in nuclear size, nuclear enlargement, hyperchromatism, and nucleolar prominence. The cardinal feature for distinction between carcinoma and PIN is that the basal cell layer is at least partially intact in PIN. The grade of the cytologic changes is usually paralleled by an increased extent and frequency of disruption of the basal cell layer (Bostwick and Brawer 1987; Amin *et al.* 1994).

INCIDENCE AND LOCATION

Premalignant lesions are those that occur more frequently in sites with carcinoma than in sites without carcinoma (Brawer 1992). The incidence of PIN is exceedingly high in prostates with cancer compared with prostates without cancer, as shown by several studies (McNeal and Bostwick 1986; Kovi *et al.* 1988; Troncoso *et al.* 1989). In particular, grade 3 PIN (by three-grade system) is found between 6% and 90% (mean, 54 %) of prostates with invasive carcinoma, and is rarely found without invasive carcinoma (mean, 17%; range, 5% to 32%) (McNeal and Bostwick 1986; Kovi *et al.* 1988; Oyasu *et al.* 1986; Troncoso *et al.* 1989). For grade 2 PIN, the findings are more variable than those for grade 3 PIN: 22% or 19% in prostates without carcinoma and 39% or 13% with carcinoma by two different studeis (McNeal and Bostwick 1986; Troncoso *et al.* 1989).

PIN is predominantly found in the peripheral zone where most of the carcinoma arises. A study of radical cystoprostatectomy specimens revealed that PIN was the most prevalent in the peripheral zone (86% incidence), with subsequently high incidence in the central zone (13%) and the lowest incidence in the transition zone (1%) (Troncoso *et al.* 1989). Thus, transition zone carcinoma does not appear to be associated with PIN (Brawer 1992).

The incidence of PIN may also be related to the thoroughness of specimen sampling and to the age of the patient. In an autopsy study of 152 men aged 10 to 49 years who died of trauma, PIN was found in 9% of those between the ages of 20 and 29 years, 22% in those 30 to 39 years, and 44% in those 40 to 49 years (Sakr *et al.* 1993a). The majority (86%) of the cases showing PIN were low-grade, and in all cases showing high-grade PIN, concurrent carcinomas were present. In another study that used whole prostate specimens, PIN was present in 45% of men aged 50 to 59 years, 52% of men aged 60 to 69 years, 37% in men aged 70 to 79 years and 38% in men aged 80 years or more (McNeal and Bostwick 1986). These findings suggest that the peak incidence of PIN precedes that of invasive carcinoma.

GRADING OF PIN

Although PIN was initially graded with a three-grade system suggested by McNeal and Bostwick (1986), participants in a recent consensus meeting on prostatic dysplasia elected to use

Table 1. Criteria for grading prostatic intraepithelial neoplasia

	Low grade	High grade
Basal cell layer	Intact	May be disrupted
Architecture	Cell stratification, crowding, and irregular spacing	Cell stratification and crowding, with micropapillary, tufting or cribriform patterns (rarely flat)
Chromatin	Slight irregularities	Irregular, clumping often with peripheral margination
Nucleus	mild nucleomegaly with anisonucleosis	Marked nucleomegaly with less anisonucleosis
Nucleolus	Small, rarely prominent	Large and prominent

a two-grade system: low grade (formerly grade 1) and high grade (formerly grades 2 and 3) (Drago *et al.* 1989). The histologic criteria for grading are primarily based on cytologic features and are summarized in Table 1. Epithelial cells in PIN of either grade show stratification and crowding. Hyperchromatism and prominence of nucleoli are additional findings in high-grade PIN. In high-grade PIN, the cells are also more proliferative than those in low-grade PIN, resulting in a wide range of architectural patterns. Four patterns that are reminiscent of patterns found in intraductal carcinoma of the breast have been described (Bostwick *et al.* 1993). These patterns include tufting, micropapillary, cribriform, and flat (Fig. 1-4) and may often coexist, although one pattern can dominate. Familiarity with this architectural diversity facilitates the recognition of PIN, but these different patterns have no predictive value for subsequent carcinoma. Morphologic changes in low-grade PIN are limited to superficial lumenal cells, which are enlarged, demonstrate anisonucleosis and slightly irregular chromatin and have small, inconspicuous nucleoli (Fig. 5). High-grade PIN shows enlarged nuclei with increased chromatin content, some irregularities and large, prominent eosinophilic nucleoli (Fig. 6, 7). The presence of large prominent nucleoli distinguishes high-grade PIN from low-grade PIN, and the preservation of the basal cell layer distinguishes high-grade PIN from invasive carcinoma.

DIFFERENTIAL DIAGNOSES

Many benign and malignant conditions need to be differentiated from PIN (Table 2). Benign conditions causing possible diagnostic confusion are seminal vesicles (Fig. 8) and ejaculatory ducts, normal central zone epithelium, benign prostatic hyperplasia, clear cell cribriform hyperplasia, atypical basal cell hyperplasia, tran-

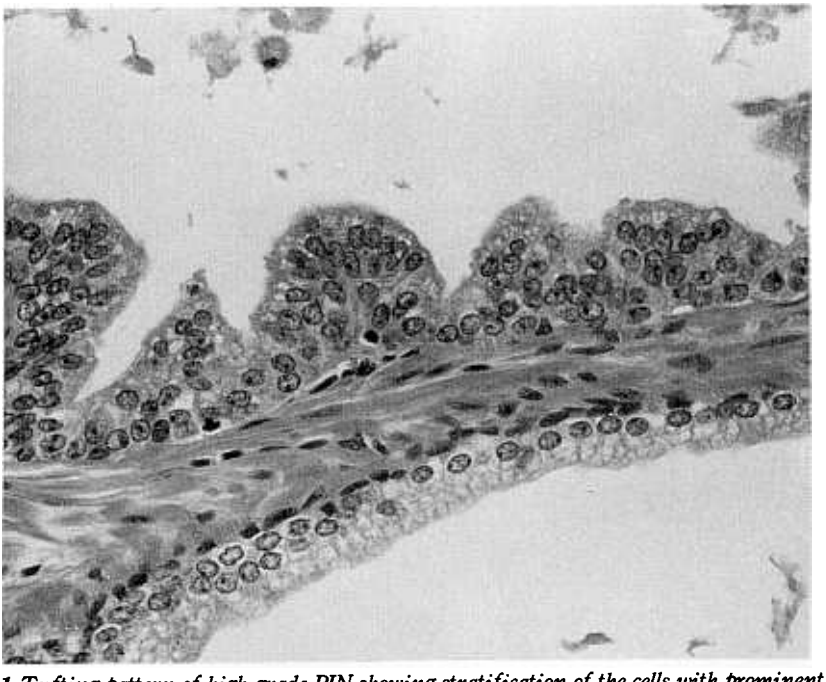

Fig. 1. *Tufting pattern of high-grade PIN showing stratification of the cells with prominent nucleoli and hyperchromasia. This is the most common pattern of high-grade PIN. Note the coexisting flat pattern of high-grade PIN in the lower half of the picture.*

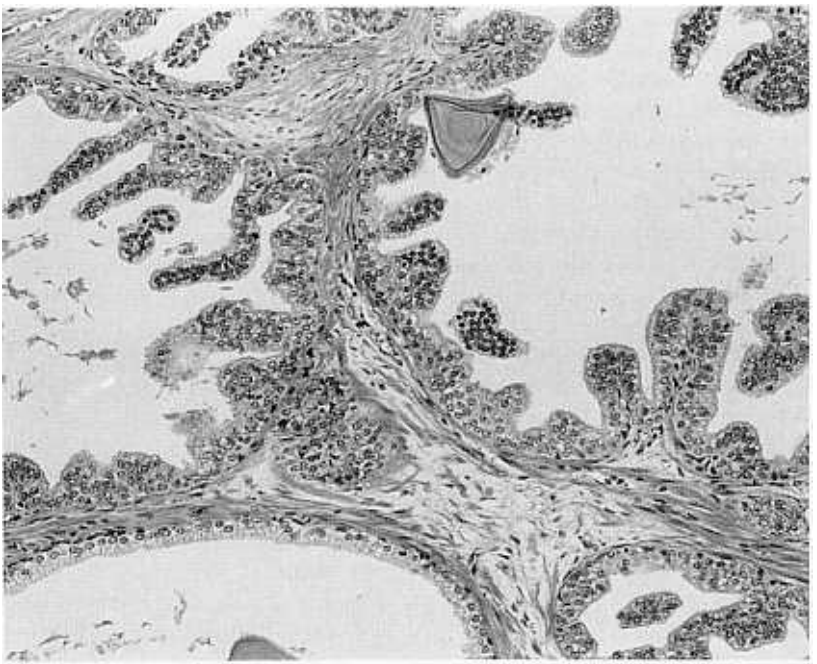

Fig. 2. *Micropapillary pattern of high-grade PIN. Note the central fibrovascular cores within the micropapillae.*

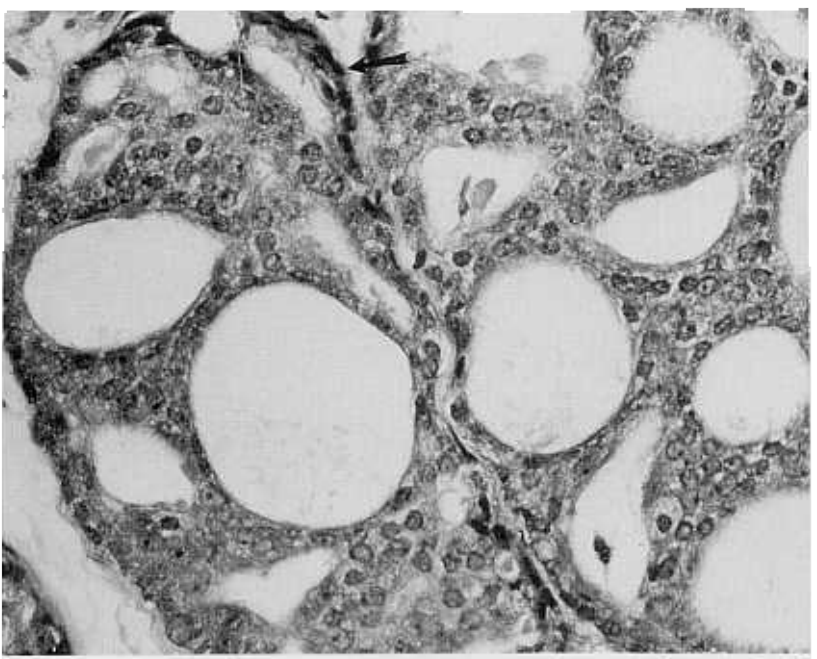

Fig. 3. *Cribriform pattern of high-grade PIN. Dysplastic cells form cribriform glands. Note the distinct basal cell layer (arrow), which is the main feature differentiating cribriform high-grade PIN from cribriform carcinoma.*

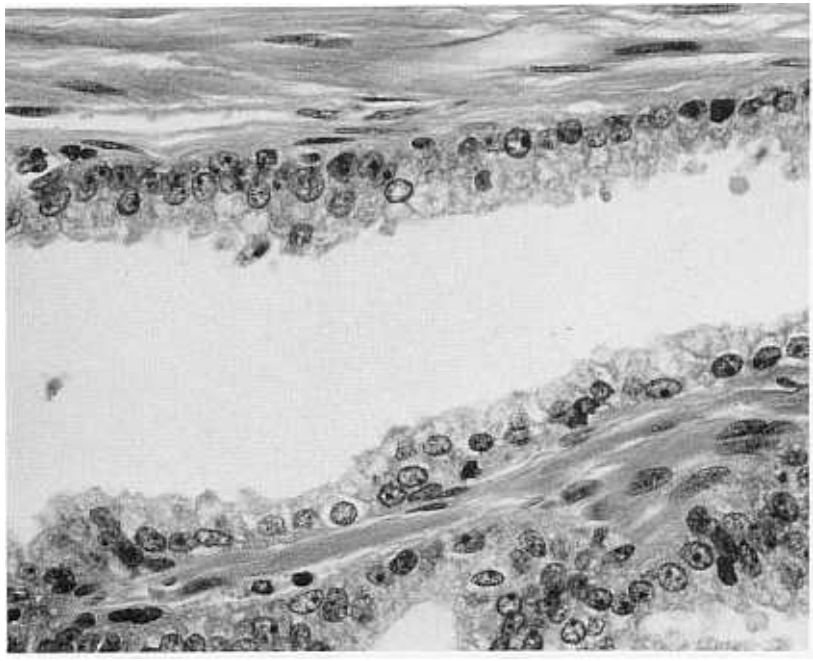

Fig. 4. *Flat pattern of high-grade PIN showing dysplastic cells in one or two cell layers with no apparent stratification.*

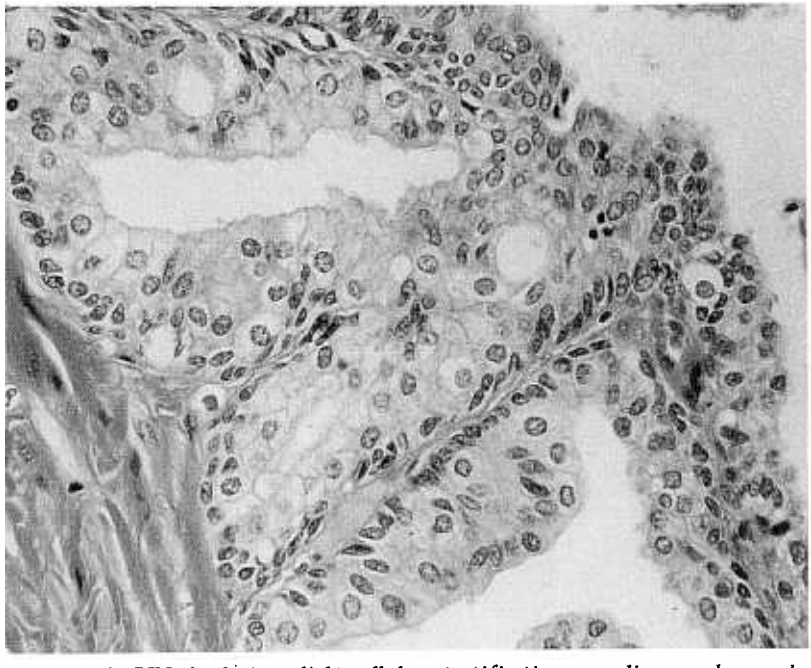

Fig. 5. *Low-grade PIN displaying slight cellular stratification, crowding, nucleomegaly, mild chromatin irregularities, and occasionally indistinct small nucleoli.*

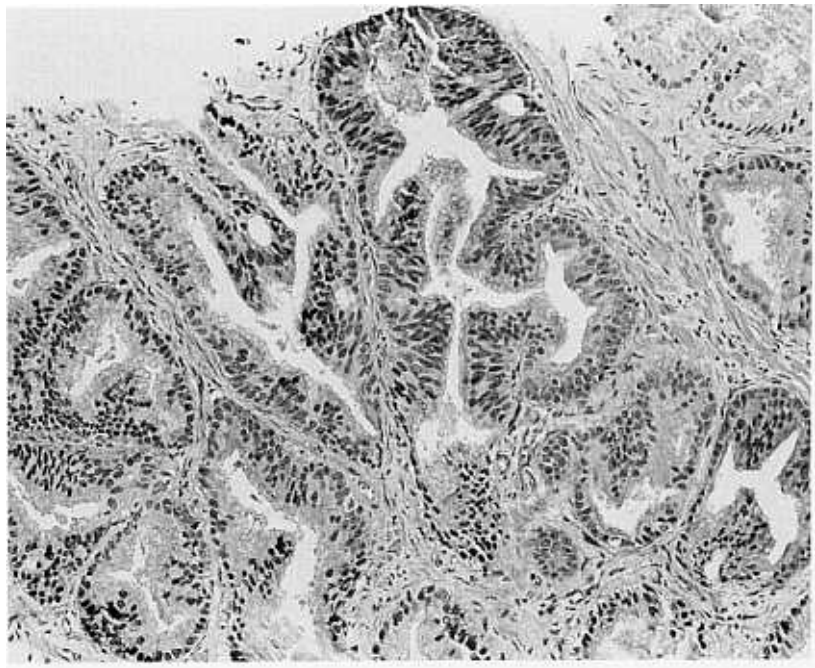

Fig. 6. High-grade PIN showing cellular stratification and crowding with hyperchromatic nuclei.

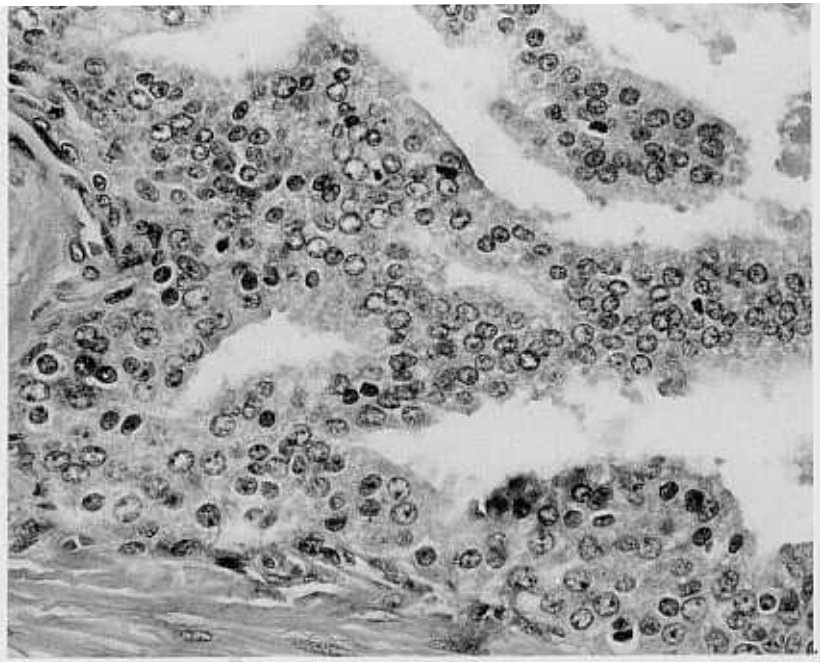

Fig. 7. High-grade PIN at high magnification demonstrating prominent nucleoli and coarse chromatin.

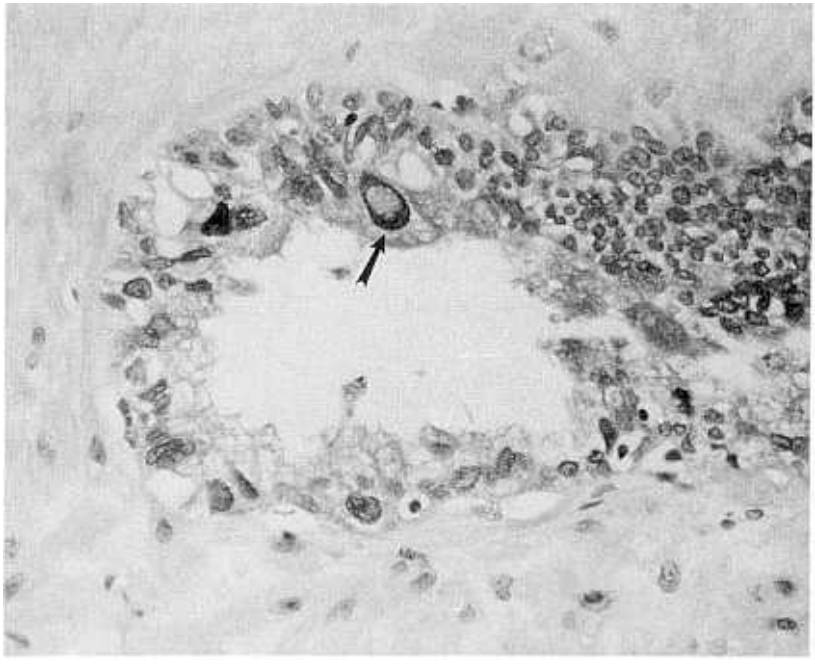

Fig. 8. *Seminal vesicle showing pronounced anisonucleosis, nuclear hyperchromasia, and characteristic monstrous cells (arrow) with an intranuclear inclusion. Lipochrome pigments are also frequently observed.*

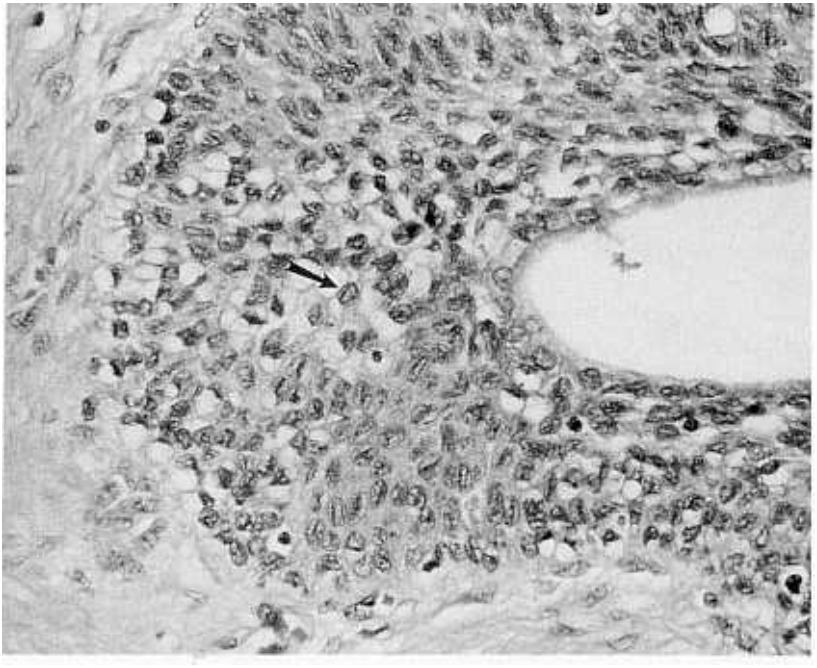

Fig. 9. *Transitional cell metaplasia showing bland nuclear features and characteristic longitudinal nuclear grooves (arrow). Nucleoli are not present.*

Table 2. Differential diagnoses of PIN

Normal/Benign Conditions	Malignancy
Seminal vesicles/ejaculatory ducts	Cribriform carcinoma
Normal central zone epithelium	Endometrioid carcinoma
Benign prostatic hyperplasia	TCC involving prostatic ducts and acini
Atypical basal cell hyperplasia	
Transitional cell metaplasia	
Atypia associated with inflammation, infarction and radiation	
Clear cell cribriform hyperplasia	

TCC, transitional cell carcinoma

Table 3. Differential features between PIN, cribriform carcinoma and ductal carcinoma

	PIN	Cribriform carcinoma	Ductal carcinoma
Basal cell layer	Intact	Absent	Absent
Proliferating cells	Columnar	Cuboidal	Columnar
Maturation effect	Present	Absent	Absent
Back-to-back arrangement	Absent	Present	Present
Fibrovascular core	Usually absent	Absent	Present
Comedonecrosis	Usually absent	May be present	Present
Zonal involvement	Peripheral	Peripheral	Periurethral
TURP diagnosis	Infrequent	Infrequent	Frequent

TURP, transurethral resection of the prostate.

sitional cell metaplasia (Fig. 9), and atypia related to radiation, infection and inflammation. Figure 10 displays atypia which is associated with inflammation. In small biopsy samples, normal epithelium in the central zone may mimic low-grade PIN. The central zone epithelium (Fig. 11) shows stratification of centrally located nuclei with intraluminal bridges and trabeculae and compact stroma that has increased amounts of smooth muscle around the glands, compared with the loose stroma found in the peripheral zone. The central zone is more frequently encountered in biopsy samples taken from the base of the prostate. The origin of the biopsy as well as the presence of other histologic features of the central zone, should aid in the recognition that "epithelial atypia" is a normal finding in this location. However, it should be remembered that PIN may occur in the central zone. The significance of PIN occurring in the central zone is currently uncertain but, we believe that PIN in this zone is not closely associated with carcinoma because carcinoma of the central zone is rare compared to the frequency of PIN. Benign prostatic hyperplasia can be differentiated from low-grade PIN by the absence of nucleoli, anisonucleosis, nucleomegaly, or nuclear chromatin abnormalities. Clear cell cribriform hyperplasia usually occurs in the transition zone, and although it has cribriform architecture simulating PIN, it lacks cytologic abnormalities (Fig. 12).

Atypical basal cell hyperplasia can mimic PIN because it shows stratification, hyperchromatism and relatively prominent nucleoli (Fig. 13). Atypical basal cell hyperplasia, however, is a condition seen in the transition zone and is composed of relatively small, less uniform, and more angulated nuclie. Immunohistochemical staining by high-molecular-weight cytokeratin (34βE12)

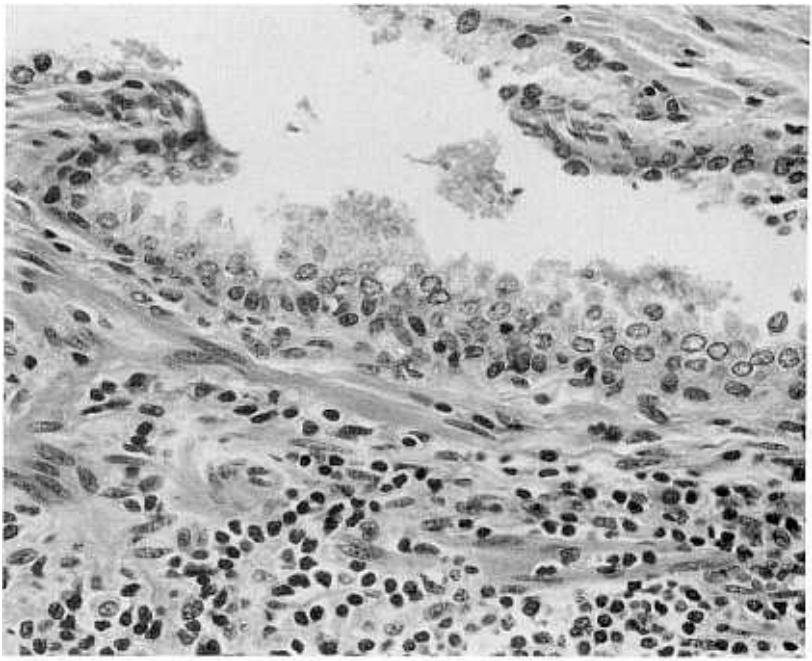

Fig. 10. *Inflammation-associated atypia. Nucleomegaly with prominent nucleoli may be seen.*

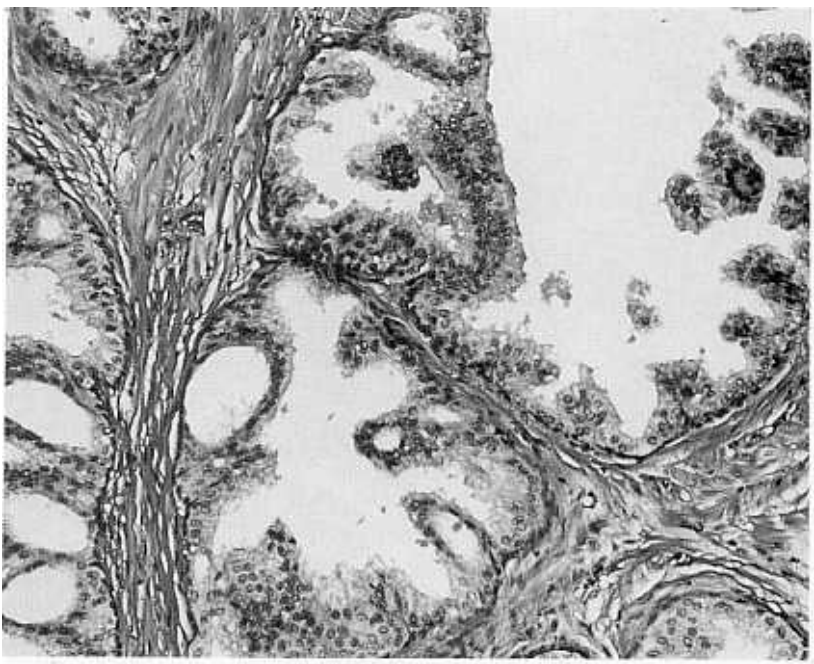

Fig. 11. *Normal central zone epithelium, which can be confused with high-grade PIN because of the architectural complexity of the intraluminal bridges/trabeculae.*

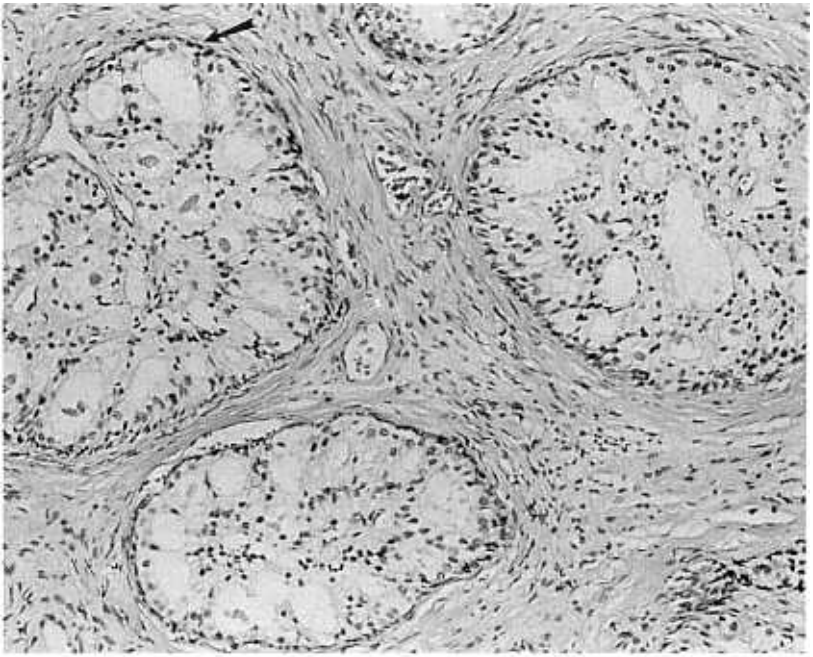

Fig. 12. *Clear cell cribriform hyperplasia showing clear cells with distinct basal cell layers (arrow) and no cytologic atypia.*

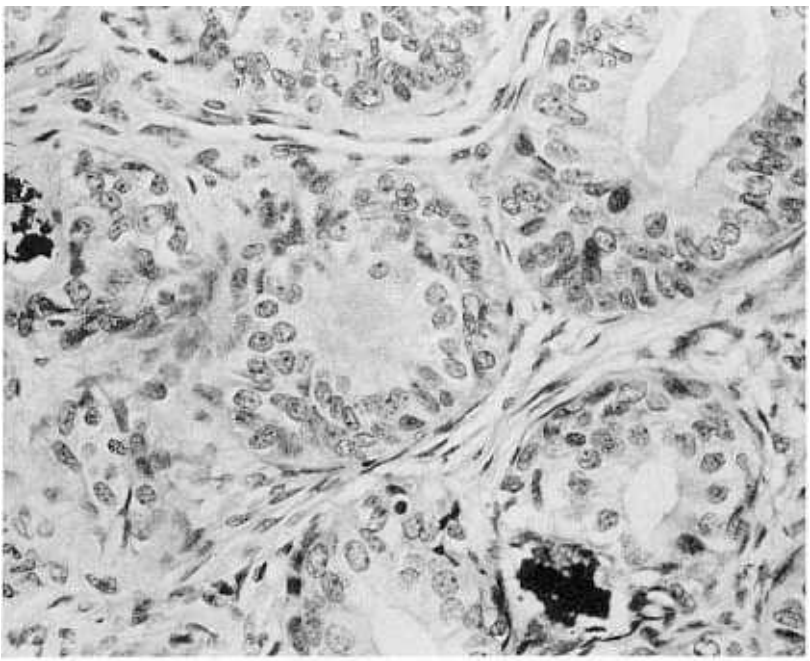

Fig. 13. *Atypical basal cell hyperplasia resembling PIN because of cellular stratification and relatively prominent nucleoli.*

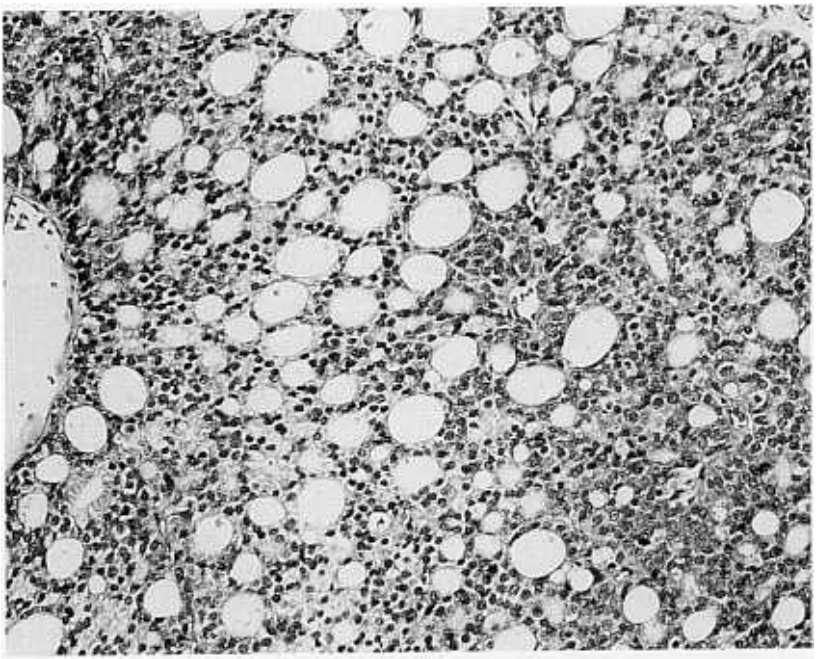

Fig. 14. *Adenocarcinoma with cribriform pattern (cribriform carcinoma), which can be difficult to differentiate from cribriform high-grade PIN. Neither a basal cell layer nor a maturation effect is seen in carcinoma.*

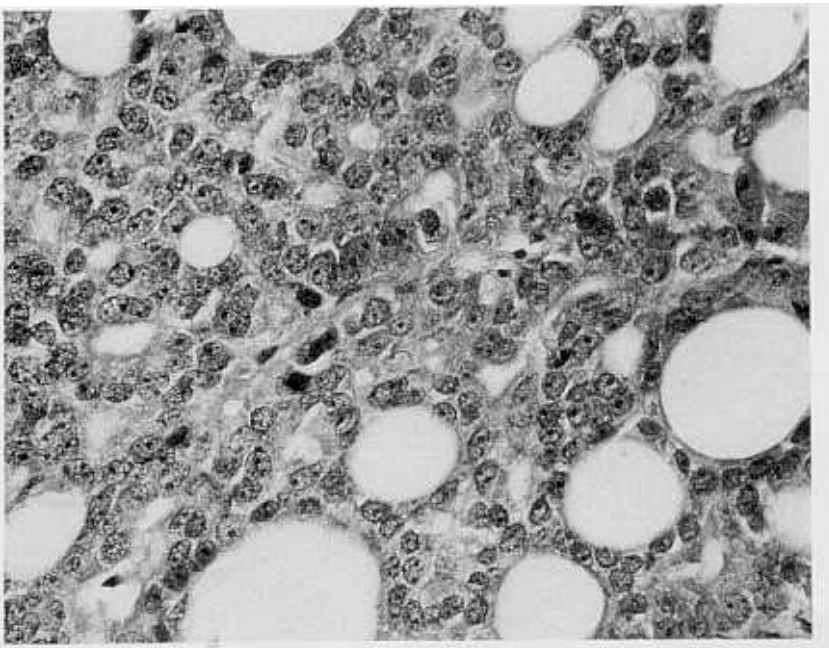

Fig. 15. *Cribriform carcinoma at high magnification showing a more complex architecture with lack of central maturation effect.*

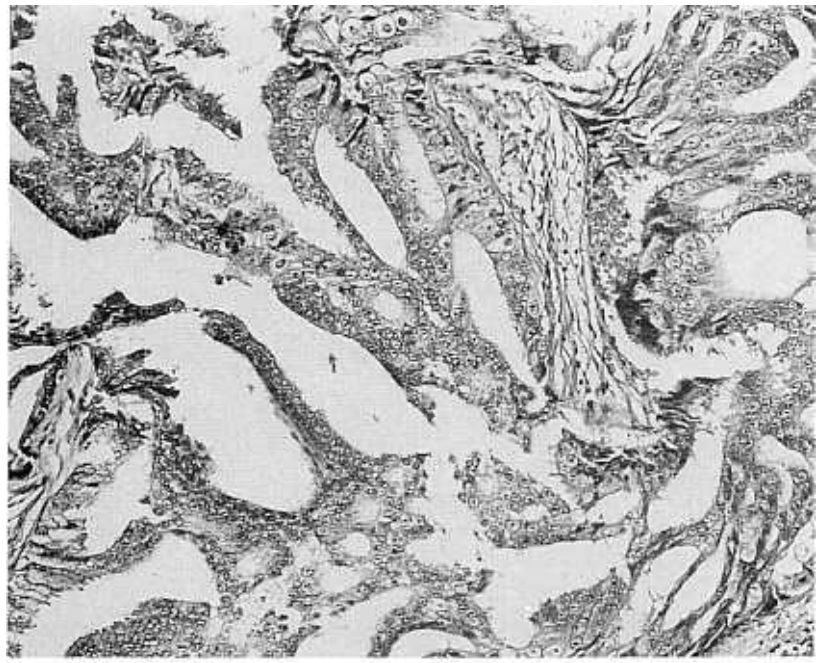

Fig. 16. *Ductal endometrioid carcinoma showing a complex architecture with a prominent intraductal component.*

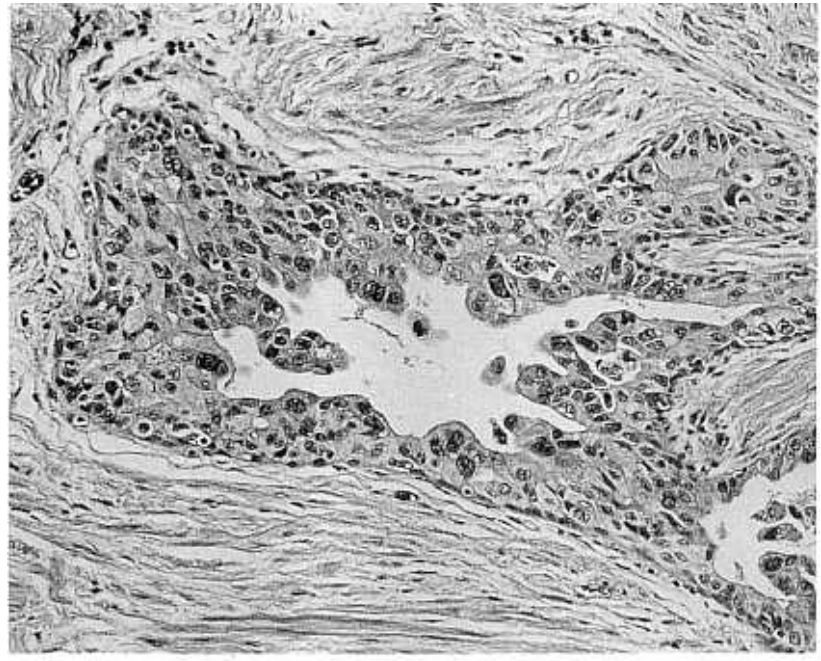

Fig. 17. *Transitional cell carcinoma involving ducts and acini. As shown here, nuclear anaplasia is usually pronounced. Mitotic figures are frequently present.*

may be useful in diagnosing difficult cases. Atypical basal cell hyperplasia reveals 34βE12 immunoreactivity in the all proliferating basaloid cells, whereas in PIN, the immunoreactivity to 34βE12 is confined to the basal cell layer beneath the negatively stained atypical nuclei (O'Malley *et al.* 1991).

Distinguishing high-grade PIN from cribriform carcinoma and ductal endometrioid carcinoma can sometimes be problematic. Differential features are summarized in Table 3. Cribriform carcinoma may be extremely difficult to distinguish from PIN that has a cribriform pattern (Fig. 14, 15). The lack of a basal cell layer is the *sine qua non* for a diagnosis of carcinoma. Another subtle feature is the tendency for atypical cells to align toward the basal cell layer and the periphery with maturation effect toward the center in PIN and complete replacement of the entire gland by atypical cells in carcinoma. Ductal endometrioid carcinoma may have an intraductal component (Fig. 16).

Transitional cell carcinoma involving ducts and acini is another lesion that is difficult to distinguish from high-grade PIN. Transitional cell carcinoma generally shows more nuclear pleomorphism and mitotic figures than does PIN (Fig. 17). Nonetheless, it can cause diagnostic confusion because transitional cell carcinoma involving ducts and acini is usually confined to the duct-acinar system and infrequently invades the stroma.

EVIDENCES FOR A PRECURSOR ROLE

Relationship of PIN to carcinoma

There is a wealth of data supporting the concept that PIN is a precursor of prostatic adenocarcinoma. Several studies, including an autopsy study and radical prostatectomy and cystoprostatectomy specimens (Kovi *et al.* 1988; McNeal *et al.* 1991; Oyasu *et al* 1986; Troncoso *et al.* 1989) have shown that the incidence, extent, and grade of PIN in prostates with carcinoma

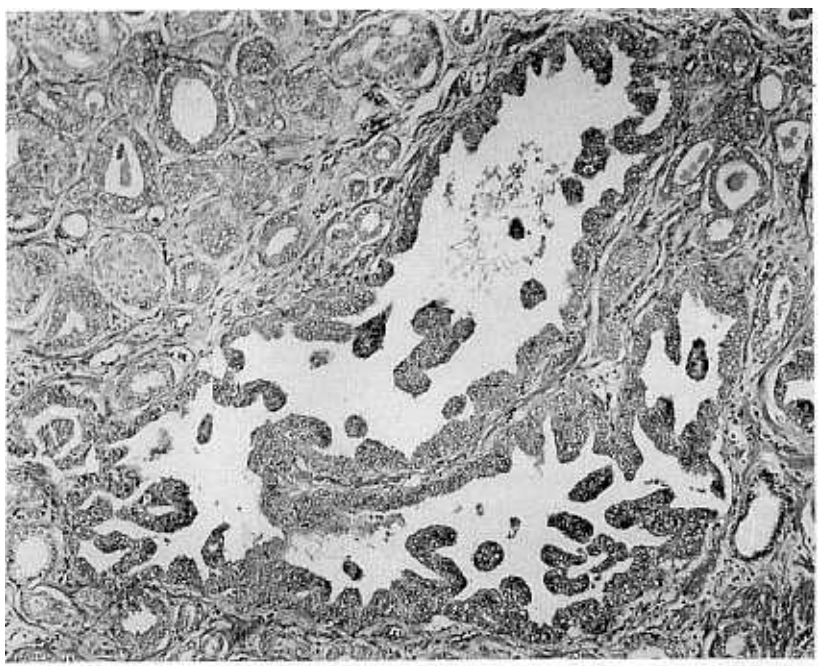

Fig. 18. *High-grade PIN in close proximity to invasive carcinoma which is seen in the left upper corner of the picture.*

are significantly higher than those in prostates without carcinoma. These findings support the contention that PIN is a precursor of prostatic adenocarcinoma. In addition, PIN, like prostatic carcinoma, usually occurs in the peripheral zone. Only 1% to 4% of PIN occurs in the transition zone (Troncoso *et al.* 1989; Oyasu *et al.* 1986) and only 14.6% of stage A cancer detected by transurethral resection of prostates have high grade PIN (Epstein *et al.* 1990). The spatial proximity of PIN to carcinoma appears to correlate with a higher grade of PIN (Bostwick *et al.* 1987; Troncoso *et al.* 1989; Fig. 18). This association of PIN and carcinoma is further substantiated by the observation of microinvasive carcinoma arising from PIN through a characteristic intermediate morphologic stage of "transitive glands" (McNeal *et al.* 1991). In addition, increasing grades of PIN correlate with increasing disruption of the basal cell layer, with an incidence of 0.7% in low-grade PIN (formerly grade 1) and 71 % in high-grade PIN (15% in former grade 2 and 56% in former grade 3 categories) (Bostwick and Brawer 1987). There are some evidences of correlation between the volume of PIN, large foci of PIN (defined as greater than one low-power microscopic field), multicentricity of PIN and the presence of carcinoma (McNeal and Bostwick 1986; Troncoso *et al.* 1989).

Evidence by morphology and histochemical/ immunohistochemical studies

PIN has many similarities to carcinoma in cytologic features. The nuclear and architectural changes portray a histologic spectrum from PIN to carcinoma. Although it has not been possible to demonstrate the histologic progression from PIN to invasive carcinoma within the same duct, the evidence is mounting that PIN represents at least one of the premalignant changes occurring in the prostate.

Evidence from several histochemical and immunohistochemical studies supports a relationship of PIN and invasive carcinoma. These include increased production of acid mucin (Humphrey 1991), increased expression of subtypes of cytokeratin (Nagle *et al.* 1991) and type IV collagenase (Boag and Young 1993; Schultz *et al.* 1993), and reduction in cytoplasmic lectin binding in PIN and carcinoma (McNeal *et al.* 1988a; Perlman and Epstein 1990). Progressive reduction of cytoplasmic immunoreactivity with PSA, prostatic alkaline phosphatase and Leu-7 with increasing grades of PIN was also observed (McNeal *et al.* 1988b). Recently, altered expression of epidermal growth factor receptor and overexpression of $p185^{erbB\text{-}2}$ and $p160^{erbB\text{-}3}$ have been noted in PIN and prostate carcinoma (Ibrahim *et al.* 1993; Myers *et al.* 1994; Sadasivan *et al.* 1993). These alterations in cytoplasmic protein composition and oncoprotein expression in the preinvasive phase of prostate carcinoma appear to herald the initiation of invasive cancer development in the prostate.

Evidence by DNA content analysis, proliferation markers and miscellaneous studies

Measuring DNA content either by image analysis or by flow cytometry may provide more objective information about the relationship between PIN and carcinoma. Studies by image analysis have reported a significant rate of aneuploidy in high-grade PIN and in carcinoma, with a wide range of values (5% to 40% for PIN and 25% to 49% for carcinoma) depending on the study (Amin *et al.* 1993a; Baretton *et al.* 1994; Crissman *et al.* 1993; Montironi *et al.* 1990; Weinberg and Weidner 1993). Flow cytometric study showed the incidence of aneuploidy was markedly lower than that shown by image analysis study. This discrepancy may be explained by the fact that image analysis allows selection of cells to be analyzed so only cells of interest are analyzed. The mean ploidy index of high-grade PIN has also been shown to be intermediate in values between benign lesions and carcinomas (Amin *et al.* 1993a).

Attempts have also been made to study the relationship of PIN to carcinoma by assessing proliferative activity using argyrophilic nucleolar organizing regions and the proliferating cell nuclear antigen (PCNA) immunohistochemistry. Studies have shown increased counts of argyrophilic nucleolar organizing regions in PIN and in carcinoma compared with those found in benign and hyperplastic epithelium (Deschênes and Weidner 1990; Sakr *et al.* 1993b). PCNA staining increased from benign prostatic hyperplasia through to carcinoma. Distinct spatial distribution of PCNA staining was also

noted; only basal layer cells expressed PCNA in benign prostatic hyperplasia, in contrast to cells in all layers of PIN and carcinoma (Montironi *et al.* 1993a). An animal study also demonstrated that expression of *ras* protooncogene mRNA was elevated in prostatic dysplasia (Yu *et al.* 1993). More recently, the frequency of apoptotic bodies (evidence of programmed cell death) has been studied, and its frequency increased from benign prostatic hyperplasia through PIN up to prostatic adenocarcinoma (Montironi *et al.* 1993b). All these aforementioned findings indicate that impairment of regulatory control culminates with advancing stages of prostatic carcinogenesis.

CLINICAL AND PRACTICAL SIGNIFICANCE OF PIN

Although there is a sizable body of evidence supporting that PIN is a premalignant condition as discussed above, the significance of PIN is not yet conclusive and should be cautiously implemented in clinical practice. Previous studies have shown that only high-grade PIN is strongly associated with carcinoma and that no statistically significant correlation has been found between low-grade PIN and the presence of coincident carcinoma (McNeal and Bostwick 1986; Sakr *et al.* 1993a). In addition, there is no documented correlation between the presence of PIN and the amount of cancer, although the volume of PIN has been correlated with the presence of carcinoma. It is not known whether all PIN lesions progress to invasive carcinoma or whether some regress. Furthermore, the time interval from the development of PIN to the development of invasive carcinoma is not yet known, although it may precede invasive carcinoma by 6 to 7 years (Kovi *et al.* 1988). In one study, patients in a long-term follow-up for PIN showed no evidence of carcinoma (Keane *et al.* 1990). Furthermore, some investigators have suggested that PIN may possibly represent an epiphenomenon rather than the cause of disease (Murphy 1991) or that it is merely an extension of cancer into adjacent ducts, so-called "pagetoid" spread (Kovi *et al.* 1985).

The exact natural history and clinicopathologic significance of PIN are yet to be resolved. Nevertheless, there is general consensus that the presence of PIN found on needle biopsy or from transurethral resections of prostates justifies all available tissue being submitted for microscopic examination. Serial sections of any suspicious areas may also be needed. Recognizing low-grade PIN is difficult and often subjective. Although only high-grade PIN is likely to be biologically important to patients, documentation of low-grade PIN in the pathology report may be useful for future studies, but at this time it has been recommended that only high-grade PIN be included in pathology reports (Amin *et al.* 1993b; Amin *et al.* 1994). The pathologist should also indicate the extent of PIN in single or multiple biopsy specimens.

Some patients with high-grade PIN can present with an elevation of serum PSA level and the hypoechoic area on transrectal ultrasound, indistinguishable from carcinoma. Although the study by Ronnett *et al.*(1993). suggested that high-grade PIN alone does not account for elevated serum PSA levels, it remains to be proved whether PIN is associated with elevated levels of PSA or whether elevated levels of PSA simply reflect the presence of coincident occult carcinoma (Brawer *et al.* 1991; Ronnett *et al.* 1993). In addition, whether PIN actually represents the hypoechoic density on ultrasound or whether other lesions induce the change needs to be further investigated. The relationship of these findings and how patients with them are managed are controversial. However, regular and long-term follow-up of such patients is clearly warranted because the finding of high-grade PIN alone may indicate the presence of a carcinoma near the biopsy site. It is generally accepted that radical therapy for PIN alone is not indicated, but a repeat biopsy under ultrasound guidance is recommended for patients with high-grade PIN to detect any occult cancer (Brawer 1992; Quinn *et al.* 1990; Bostwick 1988; Weinstein and Epstein 1993). A negative biopsy warrants close surveillance and follow-up with digital rectal examination, serum PSA assay and transrectal ultrasound done every 6 months for 2 years and thereafter annually for life (Brawer 1992). Because of the multifocal nature of PIN

and prostatic carcinoma, repeat biopsies should not be limited to the site where PIN was previously diagnosed but should also include other prostatic regions, particularly if abnormalities are detected on ultrasound.

In summary, high-grade PIN is a good predictive marker for the presence of prostate carcinoma. Because the evidence that it is as a precursor for carcinoma is inconclusive, further studies are needed to elucidate the definite role that PIN plays in prostate carcinogenesis and its clinical and biologic significance.

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