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Prostatic Intraepithelial Neoplasia (PIN): Current Concepts

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Abstract Prostatic intraepithelial neoplasia (PIN) represents the putative precancerous end of the morphologic continuum of cellular proliferations within prostatic ducts, ductules and acini. Two grades of PIN are identified (low grade and high grade), and high grade PIN is considered to be a precursor to invasive carcinoma. The continuum which culminates in high grade PIN and early invasive cancer is characterized by basal cell layer disruption, basement membrane disruption, progressive loss of secretory differentiation markers, increasing nuclear and nucleolar abnormalities, increasing proliferative potential, and increasing variation in DNA content (aneuploidy). Clinical studies suggest that PIN predates carcinoma by ten years or more, with low grade PIN first emerging in men in the third decade of life. The clinical importance of recognizing PIN is based on its strong association with carcinoma; its identification in biopsy specimens of the prostate warrants further search for concurrent invasive carcinoma.

Key words: cancer, dysplasia, hyperplasia, prostate, prostatic intraepithelial neoplasia (PIN)

Despite the potential importance of a premalignant phase in the natural history of human cancer, little attention has been given to the study of precursor lesions of malignancy in the prostate. Recently, two potential morphologic precursors of adenocarcinoma have been identified, referred to as prostatic intraepithelial neoplasia (PIN) and atypical adenomatous hyperplasia (AAH). These lesions display some of the features of carcinoma, but PIN lacks stromal invasiveness and AAH lacks significant cytologic atypia. High grade PIN is commonly found in association with invasive cancer, and the high predictive value of this lesion suggests that further search for carcinoma be made in cases in which high grade PIN is found on biopsy. AAH is also found in association with carcinoma, but not as commonly as PIN. In 1991, an international consensus conference group sponsored by the American Cancer Society concluded that PIN was the most likely precursor of invasive carcinoma, and that AAH should be further investigated as a possible precursor.

This report reviews the diagnostic criteria and clinical significance of PIN, including the evidence accumulated to date linking this histopathologic lesion with invasive cancer.

DIAGNOSTIC CRITERIA FOR PIN

PIN refers to the putative precancerous (dysplastic) end of the morphologic continuum of cellular proliferations within prostatic ducts, ductules, and acini [1–6]. The term PIN was endorsed by consensus at a 1989 international conference [1–7] to replace other synonymous terms used in the literature, including intraductal dysplasia [8], large acinar atypical hyperplasia [9], atypical primary hyperplasia [10], hyperplasia with malignant change [11], marked atypia [12], and duct-acinar dysplasia [13–15]. This consensus group also agreed that PIN should be divided into two grades (low grade and high grade) to replace the previous three grade system (PIN 1 is considered low grade, and PIN 2 and 3 are considered high grade) [7].

In low grade PIN, the cells within ducts and acini are heaped up, crowded, and irregularly spaced with marked variation in nuclear size (anisonucleosis) (Table 1; Fig. 1). Elongate hyperchromatic nuclei and small nucleoli are also observed, but these are not usually prominent features. The diagnosis of PIN requires a combination of both cytologic and architectural features, and lesions displaying some but not all of these features are considered atypical but not

TABLE 1. PROSTATIC INTRAEPITHELIAL NEOPLASIA (PIN): DIAGNOSTIC CRITERIA

	Low Grade PIN (Formerly PIN 1)	High Grade PIN (Formerly PIN 2 and 3)
ARCHITECTURE	Epithelial cell crowding and stratification, with irregular spacing.	Similar to low grade PIN; more crowding and stratification; 4 patterns: tufting, micropapillary, cribriform, and flat.
CYTOLOGY		
Nuclei	Enlarged, with marked size variation	Enlarged; some size and shape variation
Chromatin	Normal	Increased density and clumping
Nucleoli	Rarely prominent	Occasionally to frequently large and prominent, similar to invasive carcinoma; sometimes multiple
BASAL CELL LAYER	Intact	May show some disruption
BASEMENT MEMBRANE	Intact	May show some disruption

Modified from Bostwick and Brawer [2].

dysplastic. High grade PIN (formerly PIN 2 and 3) exhibits features similar to low grade PIN, although cell crowding and stratification are usually more pronounced, with less variability in nuclear size because the majority of nuclei are enlarged; the presence of prominent nucleoli, often numerous, is of greatest diagnostic utility (Fig. 2). We have identified four patterns of high grade PIN: tufting, micropapillary, cribriform, and flat [16].

PIN spreads through prostatic ducts in three different patterns, similar to prostatic carcinoma [5,17]. In the first pattern, neoplastic cells replace the normal luminal secretory epithelium, with preservation of the basal cell layer and basement membrane. Foci of high grade PIN are usually indistinguishable from ductal spread of carcinoma by routine light microscopy in our experience, although some authors claim that this distinction is possible [18]. In the second pattern, there is direct invasion through the ductal or acinar wall, with disruption of the basal cell layer and the basement membrane. In the third pattern, neoplastic cells invaginate between the basal cell layer and columnar secretory cell layer ("pagetoid spread"), a very uncommon finding.

PIN AND CANCER OCCUR COMMONLY IN THE PERIPHERAL ZONE

The peripheral zone of the prostate, the area in which the majority of prostatic carcinomas occur (70%), is also the most common location for PIN [19]. Cancer and PIN are frequently multifocal in the peripheral zone, indicating a "field" effect similar to the multi-focality of transitional cell carcinoma of the bladder. The transition zone and periurethral area, the anatomic areas in which nodular hyperplasia occurs, account for about 20–25% of prostate cancers and harbor foci of PIN in only 2% of cases [20]. By contrast, AAH is found in up to 24% of transition zone specimens [20–22]. If AAH is not a precursor of carcinoma, then the infrequency of PIN in the transition zone could account for the infrequency of cancer originating in that area.

THE BASAL CELL LAYER AND BASEMENT MEMBRANE ARE DISRUPTED IN HIGH GRADE PIN

Increasing grades of PIN are associated with progressive disruption of the basal cell layer and basement membrane [2,23–25]. Basal cell-specific monoclonal antibodies directed against high molecular weight keratin (*e.g.*, clone 34β-E12) have been employed immunohistochemically to selectively label the prostatic basal cell layer [2]. Tumor cells consistently failed to be decorated with this antibody, whereas normal prostatic epithelium was invariably stained, with a continuous intact circumferential basal cell layer observed in most instances. Basal cell layer disruption was present in 56% of cases of high grade PIN, and more commonly in glands adjacent to invasive carcinoma than in distant glands. Also, the amount of disruption increased with increasing grades of PIN, with loss of more than one-third of the basal cell layer in 52% of foci of high grade PIN [2].

The type IV collagen-immunoreactive basement membrane normally surrounding prostatic glands was focally attenuated or absent in 40% of cases of PIN [2–3]. Preliminary data have shown increased expression of type IV collagenase in PIN and cancer [26]; collagenase is a proteolytic enzyme which is thought to induce fragmentation of the basement membrane during invasion [27].

Early invasive carcinoma occurs at sites of glandular out-pouching and basal cell disruption [2,15]. Although one author has referred to this as "transitive" gland change [15], we feel that "microinvasion" is the preferred terminology as it is in other organs, avoiding introduction of a new and unnecessary term. A model of

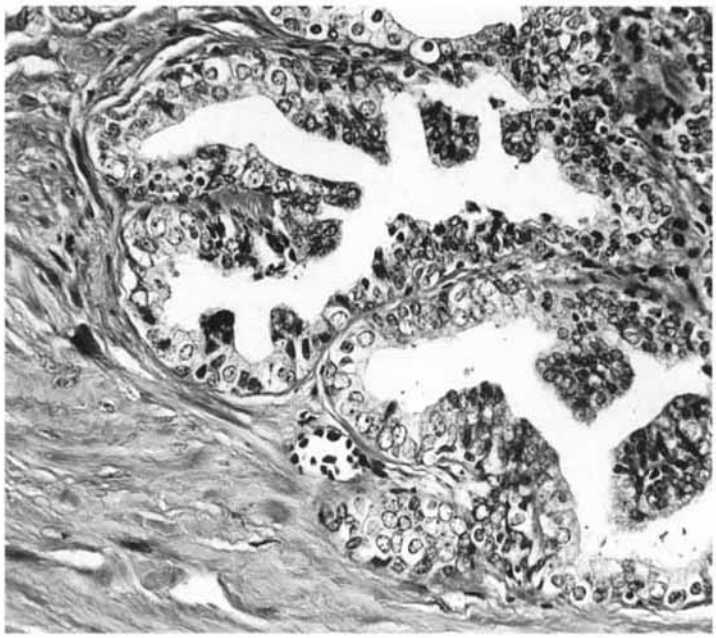

Fig. 1. Low grade PIN. The cells are crowded and irregularly spaced, with variation in nuclear size. Nucleoli are occasionally observed, but are not prominent.

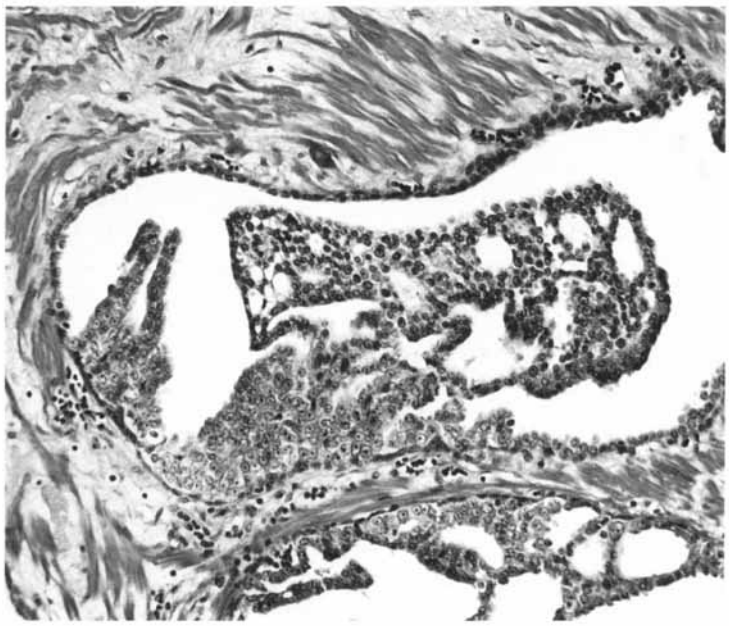

Fig. 2. High grade PIN. There is cell crowding and stratification, with nuclear enlargement and nucleomegaly. Cytoplasmic apical blebs are noted in more than 90% of cases of high grade PIN.

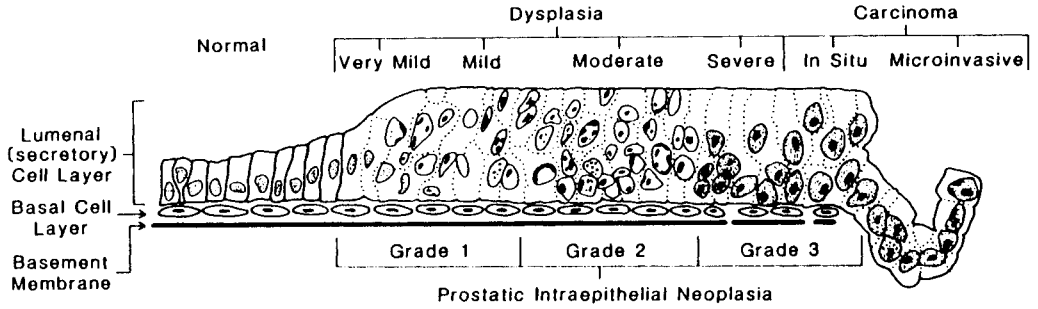

Fig. 3. Morphologic continuum from normal prostatic epithelium through increasing grades of PIN to early invasive carcinoma, according to the disease-continuum concept. Low grade PIN (grade 1) corresponds to very mild to mild dysplasia. High grade PIN (grades 2 and 3) corresponds to moderate to severe dysplasia and carcinoma *in situ*. The precursor state ends when malignant cells invade the stroma; this invasion occurs where the basal cell layer is disrupted and the basement membrane is fragmented. Notice that the dysplastic changes occur in the superficial (luminal) secretory cell layer, perhaps in response to luminal carcinogens. Disruption of the basal cell layer and basement membrane accompanies the architectural and cytologic features of high grade PIN, and appears to be a necessary prerequisite for stromal invasion.

prostatic carcinogenesis has been proposed based on the morphologic continuum of PIN and the multi-step theory of transformation (Fig. 3) [2].

THERE IS INCREASED FREQUENCY, SEVERITY, AND EXTENT OF PIN WITH CANCER

The frequency of PIN in prostates with cancer was significantly higher when compared with prostates without cancer (Fig. 4) [8–9, 28–32]. We observed PIN in 82% of step-sectioned prostates with cancer, but in only 43% of benign prostates from patients of similar age [8]. PIN was more extensive in amount in lower stage tumors, presumably due to "overgrowth" or obliteration of PIN in prostates with larger high-stage tumors [15,33].

The severity of PIN in prostates with cancer was significantly higher when compared with prostates without cancer [8].

PIN AND CANCER INCREASE WITH PATIENT AGE

In a study of 429 step-sectioned whole prostates, Kovi *et al.* found that the prevalence of PIN in prostates with cancer increased with age, predating the onset of carcinoma by more than five years [9]. A similar study by Sakr *et al.* revealed the presence of PIN in men in their

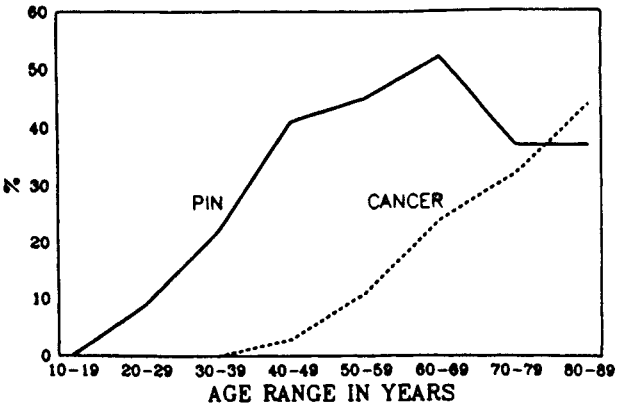

Fig. 4. Frequency of PIN and AAH in autopsy prostates. These data are from an autopsy series of 100 serially sectioned prostates with cancer and 100 prostates without cancer [8]. Note that the frequency of both of these putative premalignant lesions (PIN and AAH) is significantly increased in prostates with cancer when compared with those not harboring cancer, although PIN is significantly more common.

twenties and thirties (9% and 22% frequency, respectively), which preceded the onset of carcinoma by more than ten years (Fig. 5) [34]. Most foci of PIN in young males were low grade, with increasing frequency of high grade PIN with advancing age. The prevalence of PIN was similar in blacks and whites.

Lee *et al.* studied 256 ultrasound-guided biopsies of hypoechoic lesions of the prostate, and identified 103 cancers and 27 cases of PIN;

TABLE 2. PHENOTYPE OF PROSTATIC INTRAEPITHELIAL NEOPLASIA (PIN)

	Expression in PIN Compared with Normal Epithelium*	Expression in PIN Compared with Cancer	References
Cytoplasmic Proteins			
Prostate Specific Antigen (PSA)	Decreased	Variable	14
Prostatic Acid Phosphatase (PAP)	Decreased	Variable	14
Leu-7	Decreased	Variable	14
Pepsinogen II (PG II)	Decreased	Decreased	15
Tissue Plasminogen Activator (t-PA)	Elevated	Elevated	15
Type IV Collagenase	Elevated	Same	26
Intermediate Filaments			
Cytokeratins 14,15,16,19	Elevated	Same	37
Vimentin	Decreased	Same	37
Lectins			
Ulex Europaeus (UEA-1)	Elevated	Same	37, 38
	Decreased	Same	14, 39
Concavalia ensiformis (Con-A)	Decreased	Same	14, 39
Arachis Hypogen (PNA)	Decreased	Same	14, 39
Bandeirea simplificifolia (BS-I)	Decreased	Not evaluated	14
Dolichos biflorus (DBA)	Decreased	Same	14, 39
Glycine max (SBA)	Decreased	Same	14, 39
Triticum vulgaris (WGA)	Decreased	Same	14, 39
Len culinaris (LCA)	Decreased	Not evaluated	14
Ricinus communis (RCA-I)	Decreased	Not evaluated	14
Blood Group Antigens			
A and B	Decreased	Same	38
Le^a and Le^b	Same (negative)	Same (negative)	38
X antigen	Same (negative)	Same (negative)	38
Mucins			
Neutral Mucin	Same	Same	36
Acidic Mucin (Nonsulfated)	Elevated	Same	36

*Normal epithelium includes nodular hyperplasia.

the mean age of those with PIN (65 years) was significantly lower than those with cancer (70 years) [35].

PIN AND CANCER ARE PHENOTYPICALLY SIMILAR

There is progressive loss of markers of secretory differentiation with increasing grades of PIN, indicating progressive impairment of cell differentiation and regulatory control with advancing stages of prostatic carcinogenesis (Table 2) [13–15,36–39]. With rare exceptions, the expression of a wide variety of secretory proteins, cytoskeletal proteins, and glycoproteins is similar in PIN and invasive prostatic carcinoma, compared with normal prostatic epithelium. Nagle *et al.* suggested that changes in cytoskeletal proteins in PIN may affect transport of cell products, accounting for the differences in secretory protein distribution [37]. Recently, McNeal *et al.* have shown that reduction of cytoplasmic differentiation markers during the preinvasive phase may be followed by abrupt re-expression at the site of microinvasion [15].

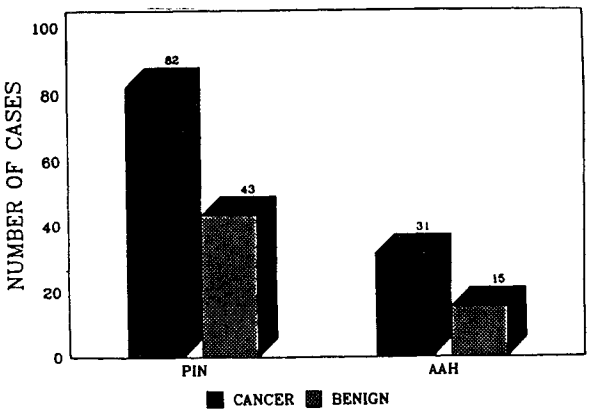

Fig. 5. Frequency of PIN and cancer with increasing age in human autopsy prostates. There is a parallel increase in the frequency of PIN and cancer, according to serially sectioned autopsy prostates, although PIN appears to predate cancer by more than 10 years. (Data on PIN from [8,34]; data on cancer curve from [21].)

PIN AND CANCER ARE MORPHOMETRICALLY SIMILAR

Virtually all measures of nuclear abnormality by computer-based image analysis revealed the similarity between PIN and cancer, in contrast

TABLE 3. MORPHOMETRIC FEATURES OF PROSTATIC INTRAEPITHELIAL NEOPLASIA (PIN)

Nuclear Features	PIN Compared with Normal Epithelium*	PIN Compared with Cancer	References
Nuclear Area	Elevated	Same	41 45
Nuclear DNA Content (Proliferation Index)	Elevated	Same	41,45
Chromatin Heterogeneity	Elevated	Same	41
Frequency of Chromatin Clumps	Elevated	Same	41
Chromatin Condensation Level	Elevated	Same	41
Chromatin Contrast	Decreased	Same	41
Nuclear Perimeter	Elevated	Same	45
Nuclear Diameter	Elevated	Same	45
Nuclear Roundness Factor	Elevated	Same	45
Nucleolar Features			
Nucleolar Diameter	Elevated	Same	40,46,47
Multiple Nucleoli	Elevated	Same	40,47
Nucleolar Eccentricity	Elevated	Same	40,47
Nucleolar Organizer Regions (AgNORs)	Elevated	Decreased	44,46

*Includes hyperplastic epithelium

with normal and hyperplastic epithelium (Table 3) [40–44]. These changes include nuclear area, DNA content, chromatin content and distribution, nuclear perimeter, nuclear diameter, and nuclear roundness. Also, most measures of nucleolar abnormality revealed the similarity between PIN and cancer, in contrast with normal epithelium [41,43,45–48]. Layfield and Goldstein found that core and needle biopsies were more reliable than fine needle aspiration in separating PIN from cancer based on a morphometric study of 50 "atypical" cases [49]. These cumulative data indicate that the morphologic continuum from PIN to cancer is characterized by progressive morphometric derangements of nuclei and nucleoli.

PIN IS FREQUENTLY ANEUPLOID

Morphologic derangements of nuclei and nucleoli observed during prostatic carcinogenesis are accompanied by progressive transformation of the normal diploid DNA content to nondiploid, according to computer-based static image analysis of tissue sections [41,45,50–52]. Montironi *et al.* suggested that two successive phases occur: the first occurs in hyperplastic epithelium and low grade PIN, and is characterized by DNA duplication without nuclear division which results in euploidy [diploid (2N) or tetraploidy (4N)]; the second occurs only in high grade PIN and cancer, and results in emergence of aneuploid elements (triploid, hyperdiploid, hypotetraploid, and aneuploid) [45]. Similar results were reported by Petein *et al.*, who noted that the mean proliferative index and proportion of aneuploid cell nuclei in high grade PIN were similar to cancer, but differed significantly from hyperplastic epithelium and low grade PIN [41]. Amin *et al.* found an incidence of 32% aneuploidy in high grade PIN and 55% in carcinoma [50], somewhat lower than the results of Crissman *et al.* (57% and 62%, respectively) [52]. Weinberg and Weidner also noted concordance of DNA content in a small series of PIN and cancer, with the majority being diploid [51].

A study of 67 cases evaluated by flow cytometry by O'Malley *et al.* revealed that aneuploidy was rare in PIN (1.8%), and that there was significant discordance of results with cancer [53]. The discrepancy in results between this flow cytometry study and the static image analysis studies of PIN may be due to sampling or other variations in methods.

ANIMAL MODELS OF PIN

Studies to date have not determined whether PIN remains stable, regresses, or progresses, although the implication is that these lesions can progress. Evidence supporting this hypothesis of progression has been obtained in animal models [54–58]. Leav *et al.* reported induction of prostatic hyperplasia, "dysplasia," and carcinoma in the Noble rat by administration of testosterone in 17β-estradiol [54]. This report suggests that dysplasia may progress to carcinoma, and that long-term hormonal stimulation plays a significant role in the genesis of these lesions.

Recent work on the aging ACI/Seg rat reveals a high frequency of spontaneous development of prostatic carcinoma [56–58]. Histopathologic studies have found sequential steps which culminate in grossly manifest prostatic cancer, indicating a developmental process. Interestingly, substantial alteration of the testos-

terone:estrogen serum ratio with malignancy supports the promotive role of steroid hormones in carcinogenesis [56].

The Lobund-Wistar rat has a 10% incidence of prostatic carcinoma with metastases when raised in a germ-free environment [55]. Recently, Pollard *et al.* demonstrated prevention of the development of primary and metastatic tumors in this rat model by feeding synthetic retinoids [*N*-(4-hydroxyphenyl)retinamide] [59].

CLINICAL EVALUATION AND SIGNIFICANCE OF PIN

The clinical importance of recognizing PIN is based on its strong association with prostatic carcinoma. Because PIN has a high predictive value as a marker for adenocarcinoma, its identification in biopsy specimens of the prostate warrants further search for concurrent invasive carcinoma (Fig. 6). This is particularly

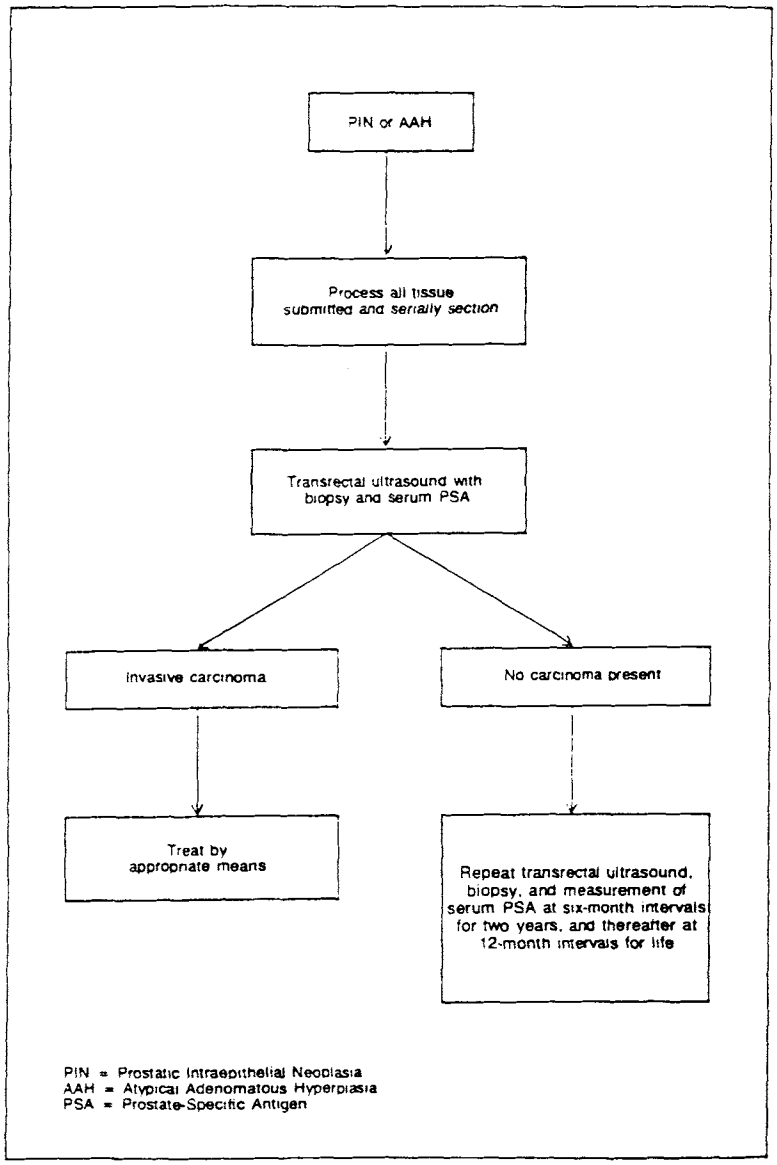

Fig. 6. Suggested diagnostic response to PIN and AAH.

true for high grade PIN; if these lesions are identified by the pathologist, close surveillance and follow-up appear to be indicated. In a series of 21 patients with PIN identified on prostate biopsy because of abnormal findings by digital rectal examination, 12 (57%) had carcinoma identified on second biopsy [60]; these results were confirmed in another study of 12 patients [61].

Carcinoma was observed in 39% of 104 follow-up aspiration biopsies of patients with an original diagnosis of PIN 3, according to Park *et al.*, and an additional 35% had recurrent PIN [62]. Of 48 patients with clinical suspicion of cancer and negative aspiration biopsies, follow-up aspiration revealed PIN in 15 (31%) and invasive carcinoma in 8 (17%). In another study of PIN diagnosed by fine needle aspiration, 13 of 32 patients with high grade PIN developed cancer as compared with 3 of 23 with low grade PIN; the patients were followed for 18 months with re-biopsy [63]. These data underscore the strong association of PIN and adenocarcinoma and indicate that vigorous diagnostic follow-up is needed. When PIN is encountered in prostatic specimens, all tissue should be embedded and made available for examination; serial sections of suspicious foci may be useful. Basal cell-specific anti-keratin antibodies such as 35β-E12 (high molecular weight keratin) can be used to stain tissue sections for the presence of basal cells. Unfortunately, needle biopsy specimens and cytologic specimens sometimes fail to show the suspicious focus on deeper levels, compounding the diagnostic dilemma.

Biopsy remains the definitive method for detecting PIN and early invasive cancer, but non-invasive methods are being evaluated. By transrectal ultrasound, PIN has been reported as being hypoechoic and indistinguishable from carcinoma [35,64]. Transrectal ultrasound-directed biopsy allows localization of the needle and tissue being sampled. Repeat biopsy has been suggested by some authors if the first attempt is unrevealing. Serum PSA levels may be elevated in patients with PIN according to Brawer *et al.* [65]. If all procedures fail to identify coexistent carcinoma, close surveillance and follow-up are indicated. Follow-up is suggested at six-month intervals for two years, and thereafter at twelve-month intervals for life [3].

The pathologist must have an understanding of the criteria for separating PIN from benign and malignant mimics, and should report the presence, severity, and extent of these lesions. Because our understanding and recognition of PIN is recent, some have suggested that only high grade PIN be reported to avoid diagnostic and therapeutic confusion, and this suggestion seems appropriate. Only through identification and reporting of premalignant lesions can further investigations be insured and periodic examinations undertaken. In difficult and borderline situations, the pathologist should communicate closely with the urologist and report as much information as possible. Most authors agree that the identification of premalignant lesions in the prostate should not influence or dictate therapeutic decisions.

PIN also offers promise as an intermediate endpoint in studies of chemoprevention of prostatic carcinoma. Recognizing the slow growth rate of prostate cancer and the considerable amount of time needed in animal and human studies for adequate follow-up, the non-invasive precursor lesion PIN would be a suitable intermediate histologic marker to indicate subsequent likelihood of cancer.

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