# E-Cadherin Expression in Prostatic Carcinoma Biopsies: Correlation with Tumor Grade, DNA Content, Pathologic Stage, and Clinical Outcome

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**We compared tumor grade and DNA content with expression of E-cadherin (E-CD), a cell adhesion molecule associated with cell-cell and cell-matrix interaction, leukocyte function, and tumor invasion and metastases, on 56 prostate carcinoma needle biopsies. The findings were correlated with final pathologic stage at subsequent prostatectomy, preoperative serum prostate-specific antigen level and further development of metastases during an initial 2.4-yr mean clinical follow-up period (range 0.5 to 5.5 yr). E-CD expression (uvomorulin, L-CAM, cell CAM 80/120, ARC-1, Sigma, St. Louis, MO) was measured by double-linked immunoalkaline phosphatase immunohistochemistry quantified with a the Roche RPW image analyzer (Roche Image Analysis Systems, Elon College, NC). DNA ploidy was determined on formalin-fixed, paraffin-embedded Feulgen-stained 5-$\mu$m tissue sections of the narrow-bore initial prostate carcinoma biopsies with the Roche RPW image analyzer. The 51% mean positive area E-CD expression in the group of 56 adenocarcinomas was significantly less than the 76% expression level for 15 normal control prostate tissues ($P < 0.001$). E-CD expression was also decreased in aneuploid (39%) *versus* diploid tumors (54%, $P < 0.001$); and in high-grade (44%) *versus* low-grade lesions (54%; $P < 0.01$). The 44% E-CD expression level in patients with metastases was lower than the 52% level in the nonmetastatic cases, but this finding was not statistically significant. On multivariate logistic regression analysis, biopsy DNA ploidy status, but not tumor grade or E-CD expression level, reached independent status ($P < 0.026$) for the prediction of metastasis. E-CD expression did not correlate with preoperative serum prostatic-specific antigen levels. We conclude that significant loss in E-CD expression can be measured in needle biopsies of prostatic carcinoma *versus* normal prostate tissue; in poorly differentiated *versus* well-differentiated tumors; in aneuploid *versus* diploid specimens; and that, although not an independent predictor of outcome, E-CD expression is of significant interest and warrants further study as a potential marker of prostate cancer development and progression.**

Key words: E-cadherin, Prostatic carcinoma, DNA ploidy.

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Microscopic tumor grading, preoperative volume estimation and clinical staging have classically served as the cornerstones for predicting outcome in prostate cancer (1–4). Increasing detection rates of early prostate carcinoma brought about by serum prostatic-specific antigen (PSA) screening and transrectal ultrasound-guided biopsies have prompted pathologists to search for newer methods of prognosis assessment that can be performed on the initial tissue specimen (5). Prostate cancer DNA content, determined both by flow cytometry and image analysis on resected specimens, has generally been successfully correlated with tumor progression, pathologic Stage D status, and poor clinical outcome (6–12). Recently the image analysis method has been applied to narrow-bore prostate biopsies with successful correlation with classic outcome predictors (13–14). A variety of oncoproteins and tumor suppressor proteins have also been studied immunohistochemically on resected specimens in a number of laboratories (10, 12, 15). The potential relationship of cell adhesion molecule expression, however, has received limited consideration in prostate carcinoma as a potential cancer progression marker that could be applied to initial needle biopsies. E-cadherin is a member of a family of calcium-dependent cell-cell adhesion receptors expressed in most normal epithelial tissues. Recently, E-CD expression loss has been associated with dedifferentiation and invasiveness in a variety of human malignancies (16–31). E-CD expression has recently been considered in resected and metastatic prostate carcinoma specimens (32–34), but E-CD levels have not been evaluated on initial prostate needle biopsies and correlated with tumor progression. In the following study we present the results of determination of E-CD expression on initial prostate needle biopsy specimens, correlate the results with biopsy tumor grade and DNA content, compare the expression levels with findings at subsequent radical prostatectomy, and correlate the expression levels

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with final pathologic stage and initial clinical follow-up in 56 men with pre-prostatectomy Stage B-2 prostatic adenocarcinoma.

## MATERIALS AND METHODS

### Patients

Fifty-six men registered on the urological oncology service of the Albany Medical Center Hospital were selected for this study. All patients were originally diagnosed with prostatic carcinoma by spring-loaded narrow-bore needle biopsies. All biopsies were fixed in 10% neutral buffered formalin and routinely processed. All patients were clinical Stage B-2 before radical retropubic prostatectomy. Formalin-fixed radical prostatectomy specimens were serially sectioned, totally embedded in paraffin, and examined microscopically. Post-prostatectomy clinical follow-up period ranged from 0.5 to 5.5 yr with a mean of 2.4 yr.

### Tumor Grading and Pathologic Staging

Tumor grade on initial biopsies was determined according to the Gleason system (2). Tumors with Gleason score of 6 or less were considered well differentiated, and tumors with scores of 7 or greater were listed as poorly differentiated. Tumors with transcapsular or seminal vesicle invasion at prostatectomy were recorded as pathologic Stage C. Patients with lymph node metastases at prostatectomy or who developed metastatic disease during the follow-up period were considered Stage D.

### Quantitative DNA Analysis

Five-micron formalin-fixed paraffin-embedded tissue sections of 56 needle biopsy specimens were stained by the Feulgen method and analyzed for DNA content using the Roche RPW image analyzer (Roche Image Analysis Systems, Elon College, NC). After routine instrument calibration against similarly stained rat hepatocytes, total DNA content histograms were prepared from the tissue sections using diploid histograms of cytologically benign nontumoral prostatic epithelial cells adjacent to the adenocarcinoma areas as internal controls. The DNA indices of the benign internal control cells were adjusted to 1.0, and the relative DNA content of the adjacent adenocarcinoma was then measured on a minimum of 100 cells with the tumor DNA index calculated by comparison with the control diploid cells. The coefficients of variation for the G0/G1 peaks of the internal diploid cells in all the tissue-section histograms ranged from 11% to 24% (mean 15%). All tumor cell histograms were reviewed without knowledge of other study parameter results and, to accommodate the relatively wide coefficients of variation of these tissue-section histograms, a DNA index of 0.77 to 1.23 was considered to be diploid. Abnormal histograms with relative DNA indices of G0/G1 peaks of the tumor cell populations greater than 1.23 were considered aneuploid. Prominent tetraploid and near-tetraploid tumor cell G0/G1 peaks were considered to be aneuploid. Histograms with tetraploid peaks <15% of total cells accompanied by diploid range G0/G1 peaks were considered to be the G2 M cell populations of diploid tumors.

### E-Cadherin Expression Level

E-CD expression level was determined by quantitative image analysis of cytoplasmic immunoreactivity in a double-linked alkaline-phosphatase–antialkaline-phosphatase technique using the Roche RPW image analyzer quantitative cytoplasmic antigen program. An additional 5-$\mu$m tissue section of the same needle biopsy block used for DNA analysis was stained by the Feulgen method, rinsed, and blocked with 20% normal goat serum. After treatment with avidin-biotin blocking reagents (Vector Laboratories, Burlingame, CA), each tumor section was stained with a monoclonal antibody against E-CD (rat IgG1 isotype clone no. DECMA-1, cat. no. U3254; Sigma Chemical Co., St. Louis, MO). Five-micron tissue sections from 15 benign prostate biopsies were stained in an identical manner for comparison. After rinsing, all sections were incubated with red alkaline phosphate chromagen (CAS red, red chromagen kit, Cell Analysis Systems, Inc., Lombard, IL) for 20 min. Sections were then washed in deionized water, dehydrated in 100% ethyl alcohol, cleared in xylene, and mounted with Fisher permount. Cell line standards of known E-CD expression were not available. The results were determined semiquantitatively as E-CD-percentage–positive area of staining intensity. To reduce background and stromal contamination, E-CD staining histograms were obtained from microscopic fields composed of predominantly tumor cells relatively devoid of stroma in the carcinoma specimens and limited to the epithelial cells in the benign specimens.

### Serum PSA Determination

Preoperative serum PSA was determined on all patients using the radioimmunoassay Tandem-R kits manufactured by Hybritech (Hybritech, Inc., San Diego, CA).

### Statistical Calculations

Statistical significance was assessed using the two-sample Student's $t$ test. The criterion for significance was $P < 0.05$. Multivariate analysis was performed using the linear regression and logistic regression models.

## RESULTS

### Biopsy Grade

Of the 56 patients with prostatic carcinoma included in this study, 43 initial biopsies (76%) were designated as low grade with a Gleason score of 6 or lower, and 13 patients (23%) displayed high-grade lesions with a Gleason score 7 or greater. The association of high tumor grade with aneuploid status on DNA analysis of the same biopsy achieved borderline statistical significance ($P < 0.06$). When the biopsies were separated into high-grade and low-grade tumor groups, there was no significant correlation between the presence of high Gleason score and tumor Stage C or D status at radical retropubic prostatectomy. Biopsy tumor grade also did not correlate with serum prostatic specific antigen level.

### Biopsy DNA Ploidy Status

Of the 56 men included in this study, 45 (80%) of the initial needle biopsy carcinoma specimens had diploid DNA patterns, and 11 adenocarcinoma biopsies (20%) were aneuploid. There were statistically significant relationships between the presence of aneuploidy in the biopsy specimen and transcapsular or seminal vesicle invasion in the 16 Stage C cases ($P < 0.03$) and with metastasis in the five Stage D cases ($P < 0.005$). Of the five patients with metastatic disease at or subsequent to prostatectomy, four cases (80%) were DNA aneuploid. No significant correlation, however, was observed between biopsy ploidy status and preprostatectomy serum PSA level.

### E-Cadherin Expression

The highest average E-cadherin expression level measured by image analysis after immunohistochemical staining was observed in the 15 benign normal control prostate specimens, which reached a 75.8% average positive staining area. The average percent-positive staining area of the 56 prostatic adenocarcinoma biopsy specimens was significantly reduced from the normal tissues to a level of 51.1% (Fig. 1). This reduction in E-CD expression in all prostatic carcinomas was statistically significant ($P < 0.001$). Figure 2 shows E-cadherin expression in prostatic biopsies as a function of presence of carcinoma, tumor grade, ploidy status, and metastatic disease. The 44.0% average positive area of E-CD expression for the 13 high-grade carcinoma biopsies was also significantly lower than the 53.3% average positive area for the 43 low-grade lesions ($P < 0.01$). Similarly, the 38.6% average positive area of E-CD expression for the 11 aneuploid biopsies was significantly lower than the 54.2% average positive area for the 45 diploid specimens ($P < 0.001$). Although the 43.8% average positive E-CD stain of the five cases with metastases was less than the 52.1% positive expression for the nonmetastatic cases, this difference was not statistically significant. Similarly, the E-CD expression level did not correlate with the serum PSA levels.

### Multivariate Analysis

Using multivariate logistic regression analysis with the diagnosis of metastatic disease (pathologic Stage D) as the end point, tumor grade again as demonstrated in univariate analysis, did not reach statistical significance ($t = 0.4$; $P = 0.699$). Biopsy ploidy status, a significant predictor of metastasis on univariate analysis, was also an independent metastasis indicator in multivariate logistic regression analysis ($t = 2.3$; $P = 0.026$). The biopsy E-CD expression level did not independently predict the presence of metastatic disease ($t = 0.8$; $P = 0.443$). Using multivariate linear regression analysis, both biopsy ploidy status ($t = -4.8$; $P < 0.001$) and biopsy grade ($t = -2.6$; $P < 0.013$) contributed significantly and independently related to the E-CD expression level.

## DISCUSSION

The national screening programs utilizing the serum PSA blood test have resulted in a substantial increase in the number of cases of early-stage prostatic carcinoma in the United States. This has prompted many laboratories to begin a survey of potential prognosis marker assessment that could be performed on initial prostatic needle biopsies that might ultimately be used to select therapy. The need for this type of initial prognosis assessment has been further accentuated by the recent reports of similar clinical outcome in men with early prostate cancer diagnosis who received no radical surgery, radiation, or chemotherapy as compared with men treated more aggressively by one or more of these modalities (35–36).

Tumor grading has long served as the hallmark for prognosis prediction in prostatic adenocarcinoma. Although many previous studies have shown direct statistically significant correlation between grading and stage, recurrence rate, and survival, these studies utilized either large-bore needle biopsy, transurethral resection, or total prostatectomy specimens (1–4). The transrectal ultrasound-guided spring-loaded biopsy, by far the most common type of initial prostate adenocarcinoma specimen evaluated by surgical pathologists today, produces a narrow-bore specimen prone to fragmentation, crush artifact, and tumor sample limitations. Recent studies have confirmed the general moderate to weak correlation between the initial grade of the needle biopsy compared to the final grade for patients who undergo subsequent radical retropubic prostatectomy (12, 37). In the present study, when stratified into low-grade cases of a Gleason score of 6 or less and high-grade cases of a Gleason score of 7 or greater, there was no statistically significant correlation between biopsy grade status and tumor stage at radical prostatectomy, or incidence of pelvic nodal or distant metastases during the clinical follow-up period. Significant correlation between tumor grade and DNA content has been well documented for prostate resection specimens (38–39). However, in our study of biopsy specimens, the trend toward correlation between high-grade tumor status and aneuploid DNA content reached only borderline statistical significance. These results indicate that the relative inaccuracy of tumor grading on narrow-bore needle biopsies significantly limits this prognosis variable in the prediction of pathologic stage at prostatectomy and subsequent clinical outcome.

Tumor DNA content analysis in the present biopsy study achieved substantial statistical prognostic significance as highlighted by the correlation with transcapsular or seminal vesicle involvement at prostatectomy and the incidence of pelvic lymph node or other distant metastases. This correlation of aneuploid status with increased rate of metastases achieved independent status on multivariate analysis. Although the majority of published studies evaluating archival resected prostatic tumoral tissue for DNA content have demonstrated a statistically significant correlation with disease outcome (7, 12, 40–45), a minority of published reports have not found ploidy status to independently predict prostatic cancer prognosis (46–48). Potential methodological sources of errors in these noncorrelating

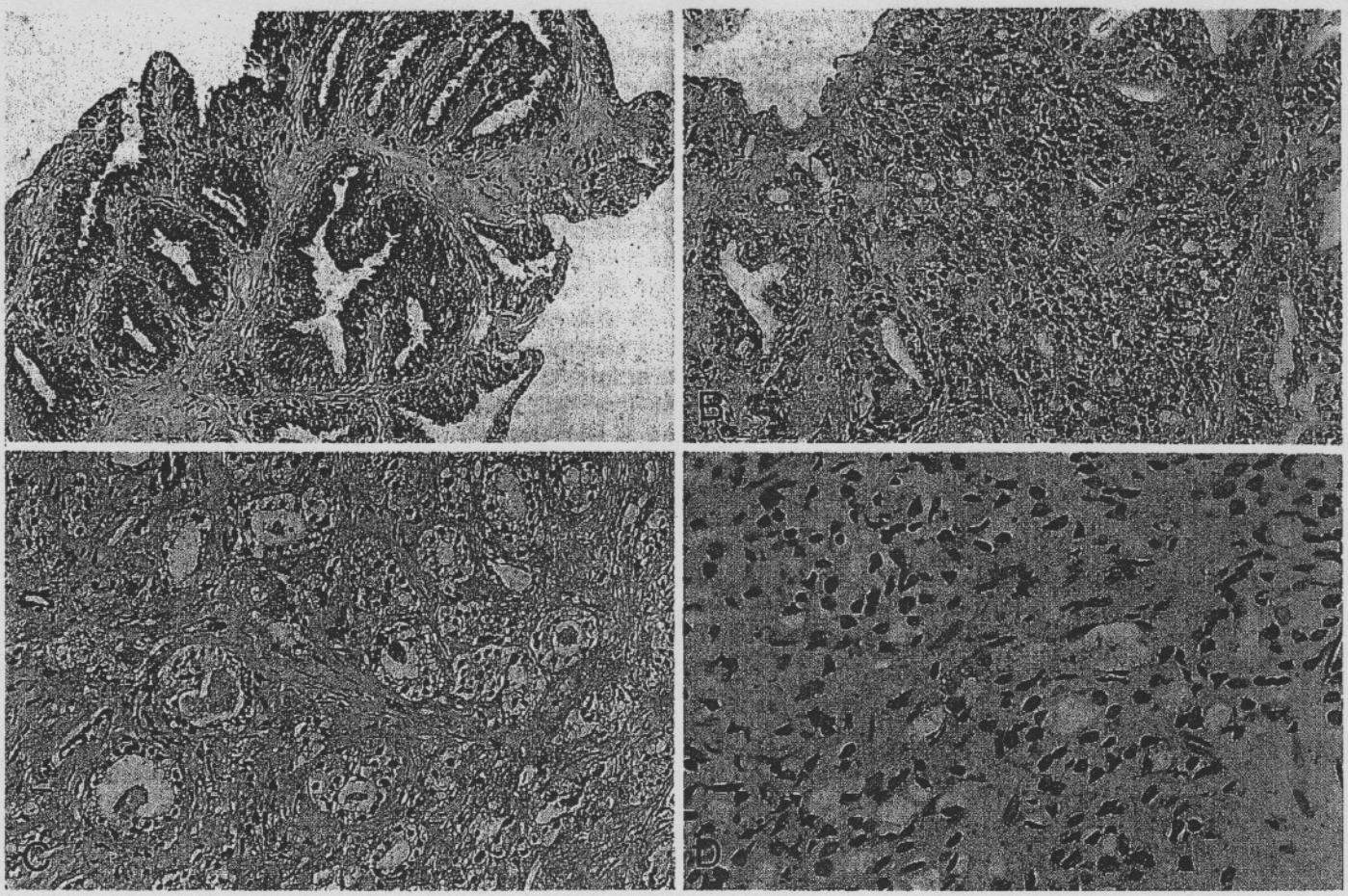

**Figure 1.** E-cadherin expression in prostate and prostate cancer. *A*: Low-power photomicrograph of normal prostate tissue demonstrating intense E-cadherin staining of acinar epithelial cells. *B*: Low-grade (Gleason score <7) prostatic adenocarcinoma demonstrating significant E-cadherin expression in tumor cells. Expression level was 64% mean positive stain. E-CD expression, however, is less than observed in typical normal prostate tissue. DNA histogram was diploid with DNA index of 1.02. *C*: Low-grade (Gleason score <7) adenocarcinoma with diploid DNA content demonstrating moderate E-CD expression with mean positive stain of 44%. *D*: High-grade prostatic adenocarcinoma (Gleason score ≥7) with significant loss of E-cadherin expression with 24% mean percentage of positive. Note relative intense staining of endothelial cells in blood vessel in center of photograph compared with prostatic carcinoma cells. DNA content was aneuploid with DNA index of 1.44 (alkaline phosphatase–anti-alkaline phosphatase; *A* to *C*, ×40; *D*, ×100).

studies of prostate cancer DNA analysis have been reviewed by Falkmer (49), and in most recent large studies with longer follow-up periods, it is widely held that ploidy significantly adds to grading on resected specimens for the prediction of future clinical course and survival (6). Finally, a relatively wide diploid range (0.77 to 1.23) was utilized in this study, reflecting the relatively wide co-efficients of variation of the G0/G1 peaks obtained from specimens cut at 5 μm and featuring relatively small numbers of cells available for analysis.

Although a variety of techniques have been used to evaluate DNA content in prostatectomy specimens, including image analysis of whole-cell fresh touch preps, tissue sections, and fine-needle aspirations, and flow cytometric analysis of fine-needle aspirations, fresh tissue disaggregation, and archival paraffin-embedded tissue disaggregations, data evaluating prospective prediction of disease outcome by DNA analysis of transrectal ultrasound-guided prostate narrow-bore needle biopsies is generally lacking in the literature. Given the small number of tumor cells available for analysis and the need to preserve tissue for permanent record, the image analysis tissue-section technique has been the preferred method for DNA analysis of prostate needle biopsies in many laboratories (13, 14). Although requiring a relatively thin (5- to 6-μm) section for nuclear separation that results in partial nuclear visualization, when tumor cell Feulgen staining intensity is compared with that of similarly sectioned benign internal-control prostatic epithelial cells, results from this method have generally correlated in an excellent fashion with whole-cell image analysis companion specimens when studied at prostatectomy (12, 50). Although potential sampling error and intratumoral DNA ploidy heterogeneity have been of concern to many investigators (51–52), excellent correlation between needle biopsy ploidy and companion follow-up prostatectomy ploidy status has been achieved (14). In summary, the DNA content analysis of prostate cancer needle biopsies can be readily determined by tissue-section image analysis, independently correlates with pathologic stage at prostatectomy, and substantially complements and exceeds *biopsy* tumor grading as an overall predictor of future clinical course.

Although serum PSA levels have been linked to prognosis variables

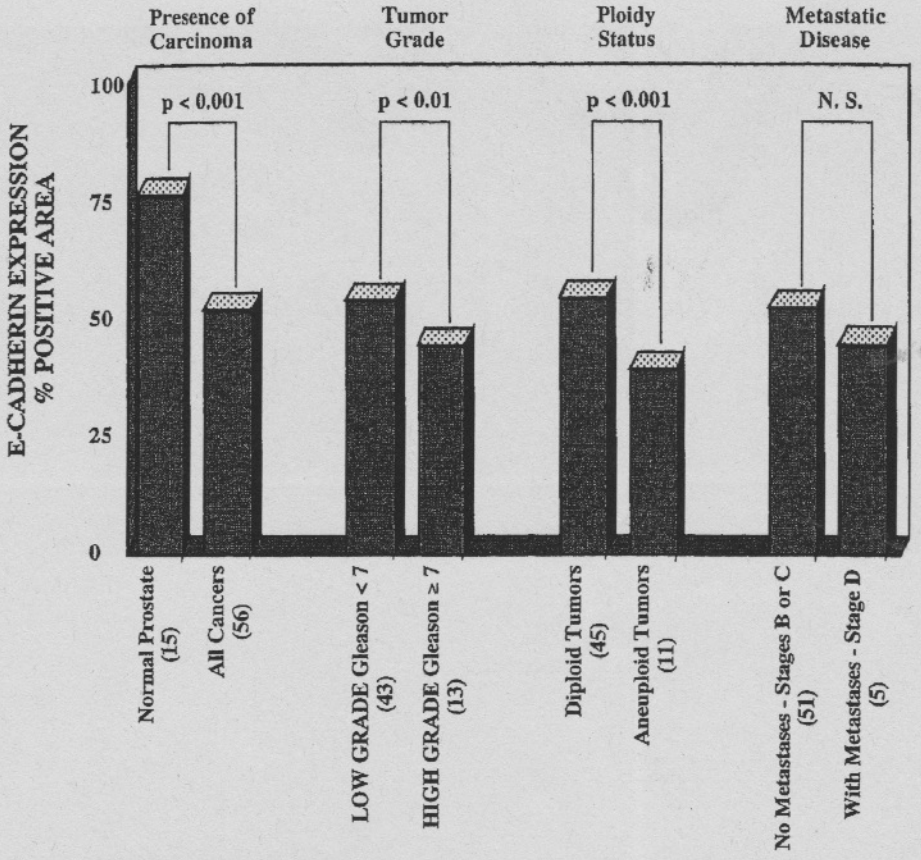


**Figure 2.** E-cadherin expression in prostatic carcinoma biopsies as a function of presence of carcinoma, tumor grade, ploidy status, and metastatic disease. Numbers of cases in parentheses.

in radical prostatectomy specimens (53), no correlation between preoperative PSA level and tumor grade, DNA content, or E-CD level was identified in the present study.

In the present study, E-cadherin, a cell adhesion molecule associated with tumor cell loss of differentiation and invasiveness, was intensely expressed in normal prostate tissues as compared with adenocarcinoma specimens. A statistically significant association of E-CD expression loss with high tumor grade and aneuploid status was achieved when quantified by immunochemistry and image analysis. However, although biopsy E-CD expression was less in cases with metastases than in localized tumors, E-CD staining did not independently predict tumor stage at prostatectomy. E-cadherin expression level measured by qualitative immunocytochemistry has previously been associated with the invasive phenotype of experimental rat prostate cancer specimens (32). In another qualitative immunocytochemical study of 84 prostate cancer primary resections and metastasis biopsies by Giroldi and co-workers, E-CD expression was significantly altered or decreased in high-grade *versus* low-grade human prostatic carcinomas, and it was suggested that E-CD expression might differentiate clinical outcome of tumors with intermediate (Gleason score 6 to 8) tumor grades (33). Interestingly, the E-CD staining level in the metastatic carcinoma foci of two patients in the Giroldi study with well-differentiated tumors was judged to be normal. In a study of 96 prostate carcinoma resection cases, Umbas and co-workers (34) found a similar statistically significant correlation between loss of E-CD expression in all prostate carcinomas *versus* normal prostate tissues, closely matching the results of the present study. Although Umbas and co-workers also suggested a correlation between loss of E-CD staining and local disease progression and metastasis, in the present study metastatic disease could not be independently predicted by the biopsy E-CD level.

The qualitation of cytoplasmic immunoreactivity by image analysis as percent-positive staining area, although generally well accepted, features several potential methodological errors that must be accounted for. Nonstaining nuclear density can lower cytoplasmic staining measurement, a problem best overcome by measuring numerous microscopic fields and utilizing a tumor or tissue with abundant and well-preserved tumor cell cytoplasm. Stromal staining can give falsely elevated results for epithelial tumors, which is best controlled by restricting the measured fields whenever possible to foci devoid of stromal contamination.

E-cadherin staining loss has been described in a wide variety of additional human and experimental neoplasms. Decreased E-CD expression has been correlated with poor survival in bladder transitional cell carcinoma (16). In breast cancer, E-CD expression has been correlated with grade and type of breast carcinomas (17) and has been implicated in the invasion and metastasis progression of ductal carcinomas (18). Interestingly, although E-CD expression significantly correlated with ploidy status in the prostate carcinomas studied in this report, E-CD expression level did not correlate with ploidy status or hormone receptor analysis in the breast cancer specimens studied by Oka and coworkers (18). It has further been reported that E-CD staining is significantly decreased in breast cancer cell lines associated with high invasion potential (19). For gastrointestinal neoplasms, E-CD expression has been correlated with dedifferentiation, progression, and metastasis in colorectal carcinoma (20, 21). Several studies have implicated loss of E-CD staining in gastric adenocarcinoma, including statistical correlation with recurrence and survival rates (22) as well as in the development of malignant peritoneal effusions (23). However, studies have not been unanimous, and Kinsella and co-workers could not correlate E-CD expression with metastasis in colorectal carcinoma cases (24). E-CD levels have also been associated with poor differentiation in head and neck squamous cell carcinoma (25), and E-CD expression loss has been demonstrated in a variety of lung cancer cell lines (26). Loss of E-CD expression has been associated with progression of premalignant papillomas to invasive squamous cell car-

cinomas in experimental skin cancers induced in mice (27), and Tohma *et al.* have reported decreased E-CD expression in poorly differentiated *versus* well-differentiated meningiomas (28). Decreased E-CD expression levels have been demonstrated in a variety of gynecological malignancies compared with their normal tissues and have also been associated with dedifferentiation in these neoplasms (29). Similarly, decreased E-CD levels have been described in metastatic ovarian carcinoma cell lines (30). Finally, loss of E-CD expression has also been attributed with high tumor grade and dedifferentiation in hepatocellular carcinoma (31).

In conclusion we have measured the E-CD expression level in human prostatic cancer transrectal ultrasound guided needle biopsies, demonstrated a significant loss in E-CD expression in prostatic carcinomas *versus* normal prostate tissue and highlighted the significant correlation of E-CD loss in high grade and aneuploid biopsies *versus* that measured in low grade and diploid cases. Although not determined to be an independent predictor of pathologic stage, the E-CD expression level on the initial prostate needle biopsy adenocarcinoma specimen is of significant interest and warrants further investigation as a potential marker of prostate cancer development and progression.

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## Book Review

### Hackel E, Westphal RG, Wilson SM (eds): Transfusion Management of Some Common Heritable Disorders, 99 pp, Bethesda, American Association of Blood Banks, 1992 ($45.00)

This volume addresses four transfusion medicine topics: An overview of hemophilia A,B and Von Willebrand's treatment, specific management of inhibitor patients, transfusion therapy of sickle cell anemia and thalassemia, and management of complications of iron overload.

Although complete with useful tables comparing available factor concentrates, the hemophilia review is disappointing in comparison to one recently published by Kasper (Transfusion 33:422–434, 1993). Products used for factor 8-deficient patients with inhibitors are included in the hemophilia B treatment table, and the dosing recommendations are not without controversy (perhaps ranges are less controversial). Discussions of each disorder are both too extensive and yet incomplete. Furthermore, the well-edited text on inhibitor treatment that follows makes the inhibitor treatment discussion in the initial chapter redundant. While treatment of the inhibitor patient with a congenital coagulation disorder is best left to a comprehensive hemophilia center, the Brettler chapter cogently summarizes both the problems and options facing the clinician treating such a patient.

The sickle cell and thalassemia discussion similarly falls short by comparison ("Sickle cell" by Wayne, Blood 81:1109–1123, 1993; and "Thalassemia" by Fosburg, Blood 76:435–444, 1990). (The article references the Blood review by Propper a decade earlier.) Discussion of the clinical features of sickle cell disease is excessive and not well weighted toward issues relevant to transfusion. Treatment of painful crises with transfusion is limited to a therapy of last resort at most centers, which is not clear from the text. The most commonly listed indication for exchange transfusion at large sickle cell centers is pulmonary sickling with consequent deoxygenation ("acute chest syndrome"), which is hardly addressed. I find confusing at best the suggestion "to immunize with a hepatitis C vaccine when it is available," made in the paragraph discussing sepsis as an indication for transfusion. Hepatitis C, as a complication of transfusion therapy, is also not otherwise addressed.

The iron overload chapter discusses pathophysiology and therapy with a balance of scientific principle and practical application and is useful for the hematologist and transfusion medicine practitioner alike.

In summary, this modest text has two well-researched and well-prepared texts combined with two disappointing papers. The former can be perused at the library, and actually purchasing this 1992 text is not recommended.

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