5'-Nucleotidase Activity in Prostatic Carcinoma and Benign Prostatic Hyperplasia

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ABSTRACT

In light of previous reports of alterations in 5'-nucleotidase activity in neoplastic conditions, 5'-nucleotidase activity was examined histochemically in tissue sections and quantified biochemically in extracts of human hyperplastic prostates and prostatic carcinomas obtained surgically. The 5'-nucleotidase activities per mg protein in extracts of 29 prostatic carcinomas were lower (P < 0.0005) than in extracts from 10 samples of benign prostatic hyperplasia. The 5'-nucleotidase activity per mg protein in extracts of prostatic carcinomas from the 29 patients correlated (R = −0.369, P = 0.049) with the degree of histological differentiation; the extracts of poorly differentiated carcinomas contained low levels of 5'-nucleotidase. When age and histological differentiation (Gleason's grade) were adjusted, the enzyme activity per mg protein correlated (R = 0.242, P = 0.004) with patient survival. When all three parameters were considered together, i.e., histological grade of the tumor, 5'-nucleotidase extracted from the tumor, and age of the patient, they were found to be mutually complementary for the prediction of patient survival (R = 0.388, P = 0.0001). To our knowledge, this is the first report that prostatic epithelium expresses 5'-nucleotidase; further work will be required to define the reasons for the high levels of activity observed in prostates without cancer and for the decrease in activity in prostatic carcinoma.

INTRODUCTION

As discussed previously (1), the system for the histological grading of prostatic carcinoma developed by Gleason and his collaborators (2–5) has been evaluated in several thousand patients and has been reproduced independently by different pathologists (6). Despite the fact that this is one of the more precise systems available for the stratification of patients with this disease, great heterogeneity exists within any recognizable subgroup of patients based on histological grade and stage. Improved systems for the stratification of patients would facilitate the development and interpretation of new therapeutic approaches to prostatic carcinoma.

With the hope that biochemical characterization might be complementary to the histopathological analysis of prostatic carcinomas, we have assayed several enzymatic activities in extracts of prostatic carcinoma (7–11); some are correlated with Gleason's grades (1, 7, 8, 10). A few of these activities in extracts of prostatic carcinoma have been more closely correlated than Gleason's grades with the survival of patients (1).

Because the 5'-nucleotidase (EC 3.1.3.5) activity has been reported to be altered in the sera of patients with some solid tumors (12, 13), we carried out a preliminary comparison of 5'-nucleotidase in prostates with and without cancer with histochemical techniques used previously in our laboratory (14). Qualitative and quantitative differences between BPH and prostatic carcinoma were observed, and enzymatic activity appeared to be expressed with greater intensity in well-differentiated tumors than in poorly differentiated tumors. Based on these observed histochemical differences, we have studied 5'-nucleotidase activity in extracts from samples of primary prostatic carcinoma and BPH. The enzymatic activity was evaluated with respect to the age of the patient, the degree of tumor differentiation, the stage of disease, and the survival of patients.

MATERIALS AND METHODS

Materials. Adenosine deaminase (VI), 5'-nucleotidase (IV), adenosine 5'-monophosphate, Trzima base, bovine serum albumin, and Folin & Ciocateu's phenol reagent were purchased from the Sigma Chemical Co. (St. Louis, MO). Sodium hydroxide, potassium sodium tartrate, cupric sulfate, and sodium carbonate were purchased from Fisher Scientific (Blawnox, PA).

Tissue Procurement. As described previously (1), prostatic tissue from transurethral resections was obtained from the surgical suite at the University Hospitals of Cleveland and from the Tissue Procurement Laboratory of the Comprehensive Cancer Center of the University of Alabama in Birmingham. Upon resection, the tissue was placed immediately in 0.9% NaCl in an ice-water bath in the surgical suite. Each chip was sliced longitudinally to obtain a sagittal section and two lateral halves. For biochemical analysis, the two lateral halves were immediately frozen and stored over liquid nitrogen at −195°C. The sagittal section was processed through paraffin or methacrylate for morphometric and histological examination. Prior to the procurement of tissue, none of the patients had received treatment with hormones or irradiation; those having undergone previous prostatic resection or orchitectomy are noted in the footnotes for Table 1. Tissue labeled carcinoma did not usually contain benign hyperplastic glands; carcinoma samples with benign hyperplastic glands that exceeded 3% of the area occupied by epithelial structures were not used.

Patients. There was some selection in our sampling of patients with benign prostatic hyperplasia that resulted from the fact that they had to be scheduled for transurethral resections of their prostates. The majority of patients with this disease do not develop symptoms that are sufficiently severe to warrant surgical therapy, and they would be excluded. Similarly, chips of transurethrally resected prostate from patients with benign prostatic hyperplasia were excluded if they contained less than 10% glandular elements as assessed by morphometric analysis or if they had significant pathological alterations other than benign prostatic hyperplasia. We do not have a record that would tell us whether or not any patients with hyperplasia were excluded from this study of 10 patients with benign prostatic hyperplasia; however, analysis of current work in our laboratory shows that two of 45 consecutive patients with benign prostatic hyperplasia were excluded from a similar study based on these criteria, one because of widespread prostatitis and one because there were no chips that consisted of at least 10% glandular elements. Having stated that few, if any, patients with hyperplasia were excluded, we should note that specific chips from many patients were excluded based on these same criteria. Among prostates from which satisfactory chips for biochemical analysis were identified, 72% of chips were considered satisfactory for biochemical analysis; 20% were excluded because they contained less than 10% glandular elements; 6% were excluded because they contained significant...
cant prostaticis; 1% were excluded because they contained squamous metaplasia; and 1% were excluded because the tissue was artifactually distorted by instrumentation to a degree that made histological interpretation uncertain or impossible.

The patients with carcinoma included in this study differed from the general population of patients with prostatic carcinoma in that they had to be scheduled for transurethral prostatic sections for carcinoma or suspected carcinoma. This would exclude a small number (we think four) of patients who had radical prostatectomies and a somewhat larger number of patients whose only surgery was a needle biopsy followed by radiation therapy; we do not know how many patients at our institution may have had a needle biopsy as the only tissue that was sampled for diagnostic purposes. Our prostatic carcinomas were not consecutive patients, and we cannot prove that they are generally representative of patients with prostatic carcinoma. A large proportion of our patients were from the Birmingham Veterans Hospital; advanced Gleason’s grades (particularly grades 8 and 9) were more common among these patients than among series that we have reviewed from University Hospitals in Birmingham and from University Hospitals of Cleveland. For that reason, we deliberately selected some patients who would represent more favorable Gleason’s grades. In addition, we excluded one patient with extensive prostatic concomitant with carcinoma and approximately 25% of the prostate that we examined that either (a) included no chips with carcinoma in the absence of benign prostatic hyperplasia (we allowed a maximum of 3% benign prostatic hyperplasia in the samples of carcinoma as assessed morphometrically) or (b) included no chips with at least 10% epithelial elements.

Histocchemistry. Tissues were embedded in glycol methacrylate at 4°C following the procedures of Beckstead et al. (15, 16) as used by us previously (14, 17, 18). The histochemical demonstration of 5'-nucleotidase was performed on methacrylate-embedded prostatic tissue according to the procedure of Wachstein and Meisel (19) in the presence of L-p-bromotetramisole oxalate to inhibit nonspecific alkaline phosphatase (20) as used by us (14, 18) previously. Sections were counterstained with 2% methyl green.

Morphometry. The percentage of epithelial elements for the sample assayed was quantified with the sagittal section of each resected chip with a Nikon projecting microscope interfaced with a HIPAD Digitizer (Houston Instruments, Austin, TX), an IBM-compatible personal computer, and Biocuant System IV software (Bioquant; R&M Biometrics, Inc., Nashville, TN) in a manner similar to that used by us previously (10).

Tissue Homogenization. The method of the homogenization of tissue was previously described (10). While still frozen, the lateral halves of a single chip were ground over liquid nitrogen to a fine homogeneous powder with a mortar and pestle that had been stored at —195°C for at least 12 h prior to the experiment. Samples of powder equivalent in weight to half a needle biopsy (Table 1) were suspended in a 1:8 dilution (w/v) with cold 0.05 M Tris buffer (pH 7.7) in an Eppendorf-stype, 1.5-ml microcentrifuge tube (No. 72.690; Sarstedt Co., Princeton, NJ). With a Tekmar TMS40 microwave homogenizer (Tekmar, Cincinnati, OH) and 5/64-inch Microtip-stepped probe, sonication of the suspension at a setting of 40% of maximum output was performed for three, 20-s periods with intervening 60-s cooling periods in an ice-water bath. The suspension was sedimented at 25,000 x g in a Beckman J-21B centrifuge (Beckman Instruments, Inc., Palo Alto, CA) for 30 min. After decanting the supernatant, the pellet was resuspended in an equivalent volume of the same Tris buffer. Sonication and centrifugation were repeated. The second supernatant obtained was combined with the first and placed in an ice-water bath before the enzyme and protein analyses were performed.

Enzyme Assay. 5'-Nucleotidase activity was determined with the coupled enzyme assay developed by Ipata (21). Briefly, 0.0145 ml of adenosine deaminase VI (10 µg/ml, 200 units/mg protein, in 50% glycerol in 0.01 M potassium phosphate, pH 6.0) was combined with 0.100 ml of 0.05 mm AMP and 0.316 ml of 0.05 M Tris-HCl buffer at a pH of 7.4 in a microcentrifuge tube suspended in a water bath at 25°C. A 0.025-ml aliquot of the enzyme-containing combined supernatant was rapidly forced into the reaction mixture which was then transferred into a 0.5-ml, 1-µm path, quartz cuvet housed in a 25°C thermostatically controlled spectrophotometer. Varying concentrations of the combined supernatant and 5'-nucleotidase were assayed against a reference cuvette in which the enzyme preparation was substituted with the homogenization buffer. Enzymatic activity was determined by the rate of change in absorbance for a minimum of 10 min with a Gilford Response 640 spectrophotometer in a kinetic mode at 265 nm. A molar extinction coefficient of 8,700 µM/cm was obtained for inosine.

Protein. The protein concentrations of the extracts were assayed by the Hartree (22) modification of the method of Lowry et al. (23). Bovine serum albumin served as the standard.

Clinical and Histological Data. Information pertaining to the ages of the patients, stages of their disease, adjuvant therapies, and survival times were obtained from their hospital records at the University Hospital and Veteran’s Administration Hospital in Birmingham, Alabama, and at the University Hospital Of Cleveland, Cleveland OH. Histological grades (Grades 2 to 10) according to the method of Gleason and his coworkers (2-5) were assigned to the individual tissue samples assayed and to all of the material resected from each patient to arrive at an overall score for the tumor. Gleason’s grades (2 to 10) were the sum of the two most common histological patterns (1 to 5) and did not incorporate clinical staging as proposed by some; clinical staging was evaluated independently.

RESULTS

Prostatic carcinoma contained less extractable 5'-nucleotidase activity than BPH (Table 1, Fig. 1)/wet weight (P < 0.002) and/mg protein (P < 0.0005). Of the extracts of prostates from 10 patients with BPH, none demonstrated less activity than 16.44 nmol inosine produced/min/mg protein. Extracts from only four of 29 prostatic carcinomas demonstrated activities higher than 16.44 nmol inosine produced/min/mg protein; the values ranged between 2.91 and 52.51 nmol inosine produced/min/mg protein.

Samples of prostatic carcinoma contained a higher percentage of epithelial elements than did samples of prostates with BPH (Table 2). Activity/wet weight and activity/mg protein showed no correlation with percentage epithelium in either BPH or prostatic carcinoma. Despite the lack of a significant correlation, histochemically, most 5'-nucleotidase activity was located in epithelial cells in both carcinoma and benign hyperplasia (Figs. 2-5); the endothelia of some blood vessels also stained intensely. Smooth muscle occasionally expressed traces of activity. When activity/wet weight and activity/mg protein were adjusted for the percentage of epithelial elements in the histological sections, the differences (P < 0.0014 and P < 0.0001, respectively) between activities in BPH and carcinoma were even more striking (Table 2). There was a greater than 5-fold difference between prostatic carcinoma and BPH when activity/wet weight or activity/mg protein was expressed as a function of percentage of epithelium. For prostatic carcinoma and BPH, there was no significant difference between the ages of the patients, weights of samples assayed, or protein extracted (Table 2).

The levels of histochemically demonstrable 5'-nucleotidase activity in the epithelial elements of the carcinomas appeared to be correlated generally with the levels of activity assayed in the extracts; however, we should mention specifically the difficulty that is associated with the precise quantification of enzymatic activity by histochemical methods. Histochemistry is always done in our laboratory with two or more sections from the same block of tissue. When the enzymatic activity was assessed with a semiquantitative method (ranked 0 to +), comparison of the activity demonstrated a higher degree of precision among serial 4-µm-thick sections than among serial

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Enzymatic activities were measured in the 25,000 x g combined supernatant. Epithelial content was measured morphometrically in the sagittal third of the same chip analyzed biochemically. Protein was determined by the Hartree (22) modification of the method of Lowry et al. (23).

Carcinoma values

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Wt. (mg)</th>
<th>Protein (mg)</th>
<th>Epithelium (%)</th>
<th>Per g tissue</th>
<th>Per mg protein</th>
<th>Per g tissue per % epithelium</th>
<th>Per mg protein per % epithelium</th>
<th>GGC°</th>
<th>GGO°</th>
<th>Stage (months)</th>
<th>Survival</th>
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<tr>
<td>86-54-01</td>
<td>55</td>
<td>23.5</td>
<td>2.54</td>
<td>13.2</td>
<td>667.9</td>
<td>16.44</td>
<td>50.60</td>
<td>1.24</td>
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<tr>
<td>87-03-01</td>
<td>66</td>
<td>223.1</td>
<td>2.72</td>
<td>11.1</td>
<td>428.3</td>
<td>16.54</td>
<td>43.39</td>
<td>1.50</td>
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<td></td>
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<tr>
<td>87-06-03</td>
<td>74</td>
<td>22.6</td>
<td>1.98</td>
<td>17.5</td>
<td>714.9</td>
<td>22.51</td>
<td>40.85</td>
<td>1.29</td>
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<td>87-08-02</td>
<td>67</td>
<td>20.8</td>
<td>2.93</td>
<td>24.9</td>
<td>584.0</td>
<td>35.64</td>
<td>23.45</td>
<td>1.43</td>
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<td>87-11-03</td>
<td>77</td>
<td>20.0</td>
<td>2.71</td>
<td>32.9</td>
<td>506.8</td>
<td>23.36</td>
<td>15.40</td>
<td>0.71</td>
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<tr>
<td>87-13-01</td>
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<td>23.5</td>
<td>1.71</td>
<td>41.0</td>
<td>731.6</td>
<td>51.73</td>
<td>17.84</td>
<td>1.26</td>
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<tr>
<td>87-15-01</td>
<td>63</td>
<td>15.8</td>
<td>1.73</td>
<td>23.8</td>
<td>600.7</td>
<td>21.94</td>
<td>25.24</td>
<td>0.92</td>
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<tr>
<td>87-21-01</td>
<td>64</td>
<td>17.8</td>
<td>1.31</td>
<td>37.4</td>
<td>422.9</td>
<td>40.04</td>
<td>11.30</td>
<td>1.07</td>
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<tr>
<td>87-26-03</td>
<td>60</td>
<td>18.0</td>
<td>1.73</td>
<td>12.5</td>
<td>812.2</td>
<td>29.39</td>
<td>64.98</td>
<td>2.35</td>
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<tr>
<td>87-27-02</td>
<td>77</td>
<td>19.9</td>
<td>1.49</td>
<td>17.2</td>
<td>303.4</td>
<td>25.32</td>
<td>17.56</td>
<td>1.47</td>
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</table>

Mean ± SD 68.8 ± 9.0 20.4 ± 2.6 2.09 ± 0.58 23.2 ± 10.7 575.6 ± 162.7 28.30 ± 11.18 30.44 ± 17.47 1.32 ± 0.44

2-μm-thick sections. We would speculate that part of the variation in the intensity of color observed among serial sections resulted from unintended variations in the thickness of sections. While the differences between sections rated as 1+ and 4+ were always obvious and correlated well with the activities in extracts, sections that differed only slightly with respect to the intensity of staining, i.e., 3+ as compared with 4+, did not show differences in extracted enzymatic activities consistent with the small differences in intensity of staining noted histochemically.

In addition to the limitations that are inherent in the precise histochemical quantification of any activity, different patterns of staining in the same section complicated the accuracy with which activity could be estimated histochemically. Tumor with different Gleason's patterns in the same section commonly showed marked differences in enzymatic activities. Most commonly, cribriform patterns demonstrated intense staining of the luminal surfaces of the apertures or pseudolumina in the cribriform patterns; however, the intensity of this staining varied from tumor to tumor and, to a lesser degree, from one cribriform area to another within the same tumor. Glandular elements of the carcinomas were also generally observed to have intense activity on the lumenal surfaces of the glands; however, heterogeneity in staining was observed and included both inter- and intratumor variations even in the context of the same Gleason's pattern. The overwhelming majority of epithelial cells that formed gland-like structures and/or cribriform structures expressed histochemically demonstrable 5'-nucleotidase; however, some did not. While the enzymatic activity was generally confined to membranes and contiguous cytoplasm facing lumenal surfaces; this pattern did show some variation. In particular, while cells in Gleason's pattern 5 generally showed low levels of activity, this activity in the epithelial cells in pattern 5 was often expressed uniformly throughout the cell.

Although the correlation between histopathological differentiation (Gleason's grade) and extracted 5'-nucleotidase was significant (R = -0.369, P = 0.049) in this small number of
Fig. 1. Enzymatic activity in benign prostatic hyperplasia (BPH, ■) and in prostatic carcinomas (□) with different Gleason's grades. Less well-differentiated carcinomas contain less extractable enzymatic activity.

Table 2 Comparison of patient and tissue parameters

<table>
<thead>
<tr>
<th>Observed</th>
<th>BPH (mean ± SD)</th>
<th>Carcinoma (mean ± SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observations</td>
<td>10</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>68.8 ± 9.0</td>
<td>68.2 ± 8.0</td>
<td>0.8648</td>
</tr>
<tr>
<td>Weight (mg)</td>
<td>20.4 ± 2.6</td>
<td>18.7 ± 2.6</td>
<td>0.0918</td>
</tr>
<tr>
<td>Protein extracted (mg)</td>
<td>2.09 ± 0.58</td>
<td>1.68 ± 0.47</td>
<td>0.0675</td>
</tr>
<tr>
<td>Percentage of epithelium in sample</td>
<td>23.2 ± 10.7</td>
<td>54.7 ± 19.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Activity/g tissue</td>
<td>575.58 ± 162.74</td>
<td>266.87 ± 272.54</td>
<td>0.0002</td>
</tr>
<tr>
<td>Activity/mg protein</td>
<td>28.30 ± 11.18</td>
<td>10.49 ± 10.20</td>
<td>0.0005</td>
</tr>
<tr>
<td>Activity/g tissue/epithelium</td>
<td>30.44 ± 17.47</td>
<td>5.51 ± 5.07</td>
<td>0.0014</td>
</tr>
<tr>
<td>Activity/mg protein/epithelium</td>
<td>1.32 ± 0.44</td>
<td>0.20 ± 0.20</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Activity of 5'-nucleotidase expressed as nmol inosine produced/min.

patients, the significance was marginal. In this context, it is of interest to note that a larger number of patients has been required in most series in order to get a significant correlation between Gleason's grade and survival. Correlations between enzymatic activity and Gleason's grades were slightly better for activity/protein than for activity/wet weight as follows: activity/protein and Gleason's grade of all tissue removed from the patient (R = -0.369, P = 0.049), activity/wet weight and Gleason's grade of all tissue removed from the patient (R = -0.361, P = 0.054), activity/protein and Gleason's grade of the chip analyzed (R = -0.326, P = 0.085), activity/wet weight and Gleason's grade of the chip analyzed (R = -0.329, P = 0.081). The higher values of enzyme activity were present in more highly differentiated tumors. Adjustments for percentage of epithelial elements did not improve the correlation with differentiation.

Variables that might influence the survival of patients with prostatic carcinoma were analyzed and P values were computed with the Cox regression model (24). Ages of the patients with prostatic carcinoma were found to correlate (R = -0.336, P = 0.0002) with survival. After adjusting for age, the Gleason's grade for the patient sample assayed correlated (R = -0.165, P = 0.028) with survival. Once age and the histological grade were adjusted, the activity of 5'-nucleotidase/mg protein showed significant correlation (R = 0.242, P = 0.004) with survival. The stages of patients' diseases were not found to correlate with survival. When multiple correlation coefficients were considered, age and Gleason's grade of the sample assayed (R = 0.337); and age, Gleason's grade of the sample assayed, and 5'-nucleotidase specific activity (R = 0.388) were notable for being mutually complementary for the prediction of survival.

DISCUSSION

To our knowledge, this is the first report that the epithelium of the prostate gland expresses 5'-nucleotidase. Smooth muscle from several organs (25) has been reported to express variable levels of 5'-nucleotidase activity. 5'-Nucleotidase in endothelium has been studied extensively (26, 27). The fact that 5'-nucleotidase was being demonstrated histochemically in our laboratory for another project (14) led us to do a pilot histochemical study that demonstrated much lower levels of activity in prostatic carcinomas than in hyperplastic prostates in the same histological sections. While there have been few studies of 5'-nucleotidase in the sera of patients, our observation that the epithelium of prostates from BPH expresses high levels of 5'-nucleotidase heightens our interest in a recent report (28).
that mean activities of 5'-nucleotidase "were higher (P < 0.05) for persons 40 years and older than for younger subjects." Very little is known about the clinical significance of elevated levels of this enzyme in sera, and one wonders if this enzyme might become elevated in the sera of patients with BPH. While 5'-nucleotidase has been studied extensively in other kinds of cells, we can only speculate about its function in the prostate. In the human lymphoid system, the 5'-nucleotidase that is anchored to the plasma membrane has been described as an important marker of the differentiation of B-lymphocytes (29). In addition to this membrane-bound 5'-nucleotidase, sometimes called "ecto-5'-nucleotidase," human lymphoid cells have been shown (30) to have a "soluble" 5'-nucleotidase that differs from ecto-5'-nucleotidase with respect to the K_m and V_max, for each of several substrates, i.e., the two enzymes appear to be quite different.

Ecto-5'-nucleotidase has been described in many kinds of cells including lymphocytes (29), endothelial cells (27), and many other kinds of cells from several species (31); there is also a cytosolic form of the enzyme that has been studied for many years in the liver (32). Histochemically, the 5'-nucleotidase activity in the cytoplasm of prostatic epithelial cells appears to be so intense in most cells as to obscure membrane staining that may be present; however, in some areas, in addition to the intense cytoplasmic staining there is clearly dark staining of the plasma membranes of the prostatic epithelial cells.

We should comment about our conclusions in view of the uncertainty involved in drawing conclusions about the value of predictors of prognosis based upon the study of 29 patients. Because of the high degree of significance observed (P < 0.0005), it seems quite certain that the activities of 5'-nucleotidase in prostatic carcinoma and benign prostatic hyperplasia are different. The correlation that we found between Gleason's grade and enzymatic activity was of only marginal significance (P = 0.049), and it is possible that the four carcinomas that contained the highest extractable enzymatic activities are not truly representative either of carcinomas with high activity or of carcinomas with their respective Gleason's grades. If these patients should not be found with a similar frequency in the general population with prostatic carcinoma, this correlation would not be valid. Similarly, the described prognostic value of assaying 5'-nucleotidase in extracts of prostatic carcinoma is based on the observation of a very limited number of patients. The fact that, in the 29 patients studied, the expression of this enzyme was histochemically associated with the formation of gland-like structures encourages us to believe that the activity of this enzyme may reflect the degree of differentiation of the tumor; however, all of our conclusions must be tested in a larger prospective study. We selected Gleason's grading system and survival as the best available indicators of prognosis; however, we should note that, in recent years, studies of 45 (33), 72 (34), 82 (35), 88 (36), and 39 (37) prostatic carcinomas supported the conclusion that ploidy as measured by flow cytophotometry is a valuable predictor of prognosis. The measurement of ploidy will become a part of our prospective study.

The facts that the extractable 5'-nucleotidase activity (a) is present at higher levels in BPH than in prostatic carcinoma,
by which the expression of this enzyme is progressively lost in human prostatic carcinomas would also seem to be of considerable interest. The survival of patients suggest that a study is needed of the expression of this enzyme.

**REFERENCES**


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