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PROSTATE SPECIFIC ANTIGEN IN THE DIAGNOSIS AND TREATMENT OF ADENOCARCINOMA OF THE PROSTATE. II. RADICAL PROSTATECTOMY TREATED PATIENTS

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ABSTRACT

Serum prostate specific antigen was determined (Yang polyclonal radioimmunoassay) in 102 men before hospitalization for radical prostatectomy. Prostate specimens were subjected to detailed histological and morphometric analysis. Levels of prostate specific antigen were significantly different between patients with and without a Gleason score of 7 or greater (p less than 0.001), capsular penetration greater than 1 cm. in linear extent (p less than 0.001), seminal vesicle invasion (p less than 0.001) and pelvic lymph node metastasis (p less than 0.005). Prostate specific antigen was strongly correlated with volume of prostate cancer (r equals 0.70). Bivariate and multivariate analyses indicate that cancer volume is the primary determinant of serum prostate specific antigen levels. Prostate specific antigen was elevated 3.5 ng. per ml. for every cc of cancer, a level at least 10 times that observed for benign prostatic hyperplasia.

Prostate specific antigen is useful as a preoperative marker because no patient with lymph node metastasis had serum levels of less than 10 ng. per ml. (4 times the upper limit of normal range). Of the patients with greater than 50 ng. per ml. two-thirds had microscopic lymph node metastasis and 90 per cent had seminal vesicle invasion.

Serum prostatic acid phosphatase levels showed a significantly weaker correlation with cancer volume (r equals 0.51) and every other pathological parameter. Of the patients 73 per cent had serum prostatic acid phosphatase levels in the normal range (0 to 2.1 ng. per ml.), including 7 per cent who had pelvic lymph node metastasis.

Postoperative prostate specific antigen values were available in 97 of 102 patients, with a mean and maximum followup of 12 and 38 months. No patient with pelvic lymph node metastasis achieved an undetectable prostate specific antigen level without adjunctive therapy (hormonal or radiation). No difference in preoperative or postoperative prostate specific antigen levels, cancer volume, seminal vesicle invasion or incidence of pelvic lymph node metastasis was seen between patients with no capsular penetration and those with minimal capsular penetration (1 cm. or less total linear extent of full thickness penetration), providing the first quantitative evidence that small amounts of capsular penetration may not be of biological or prognostic significance. (*J. Urol., 141: 1076-1083, 1989*)

In the previous study we showed that ambulatory serum prostate specific antigen (PSA) in the untreated patient was directly proportional to intracapsular and extracapsular clinical stages of prostate cancer, as well as to the Gleason grades (score) of the biopsies.[1] In the current study, using detailed histological and morphometric analyses of 102 consecutive radical prostatectomy specimens, we examine the relationship of preoperative ambulatory serum PSA to cancer volume, capsular penetration into the periprostatic fat, seminal vesicle invasion, margin-positive tissue planes, lymph node metastases, Gleason grade of the prostate cancer, prostate weight and amount of benign prostatic hyperplasia (BPH) within the radical prostatectomy specimen.

METHODS

After the seminal vesicles were removed from the base of the prostate gland, radical prostatectomy specimens were weighed and then fixed for 24 hours in undiluted formalin. Surgical margins were assessed by trimming 2 mm. sections from the distal edge of the apex and the proximal edge of the bladder neck. The outer surface of the prostate then was inked and blocked serially in 3 mm. transverse sections perpendicular to the rectal surface of the gland from the apex to the base. Sections were cut at 5 μm. from the inner surface of each block and stained with hematoxylin and eosin. The area of the cancer in each histological section was outlined precisely in ink and traced, and with a digital computer technique and Image Measure† software, the area of tumor at each 3 mm. level was determined. Volume was calculated as the sum of tumor area times the section thickness (3 mm.). If 2 or more independent tumors were identified their volumes were summed. This volume then was corrected for tissue shrinkage during processing by a previously established multiplication factor of 1.5.[2] Seminal vesicles were sectioned longitudinally in the coronal plane.

The percentage of tumor occupied by Gleason grades 3 or less, or 4 and 5 was estimated for each cancer. Complete penetration of the prostate cancer into the periprostatic fat was measured on each slide in centimeters along the length of the capsule and all lengths were summed.[2, 3] The volume of BPH in each gland was estimated by digitizing the largest area in each lobe occupied by BPH, and is presented in square centimeters.

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The Yang Pros-Check polyclonal radioimmunoassays for PSA and prostatic acid phosphatase (PAP) were determined as described previously.[1] Post-radical prostatectomy sera represent a special problem. Since PSA is organ-specific total prostatectomy should result in undetectable levels but radioisotope analytic procedures always result in some additional statistical variation in radioactive counting. Our controls, against which all post-radical prostatectomy sera are compared,[4] are post-cystoprostatectomy sera in which histological examination of the prostate at 3 mm. intervals showed no cancer. Logit-log radioimmunoassay plots permitted greater statistical accuracy at lower concentrations of PSA. Interassay mean and standard deviation for 64 determinations of these male sera in 9 different assay lots of PSA was 0.01 ± 0.03 ng./ml. Female sera are less satisfactory for post-total prostatectomy controls, not only because of reports that the paraurethral glands are immunoperoxidase positive for PSA but also because 5 per cent of all women have anti-PSA antibodies associated with vaginal irritation from the immunogenicity of PSA in human semen.[5] Interassay mean and standard deviation for 54 determinations from 7 different assay lots of PSA on a pool of 6 asymptomatic, healthy female volunteers was 0.18 ± 0.16, significantly different from the cystoprostatectomy sera ($p < 0.001$). Three standard deviations for post-cystoprostatectomy sera would be ± 0.1 ng./ml.; to assure minimal false positive results we have arbitrarily taken 3 times this upper range (0.3 ng./ml.) as indicative of residual disease, that is we have defined PSA of less than 0.3 ng./ml. as equivalent to zero (undetectable). The coefficient of variation, however, for male sera with PSA concentrations of 2.0, 1.0, 0.5, 0.4, 0.25 and 0.125 ng./ml., run 18 to 22 times each with 4 different assay kits, was 6.8, 12, 25, 39, 53 and 98 per cent, respectively.

Statistical variances are standard error unless otherwise stated. Pearson correlation coefficients were used as a measure of the linear association between any 2 variables for which a matrix of pairwise scatter plots was constructed.[6] Multivariate linear regressions were used to study the relationship between preoperative concentrations of PSA and PAP and the histomorphological measurements from the radical prostatectomy specimens.[7] Logarithmic transformations of continuous non-negative variables, such as cancer volume, were used in regression analyses and in computation of Pearson correlation coefficients. The constant 0.25 was added to variables with values near or equal to zero on some patients before logarithmic transformation to prevent logarithmic numbers of less than zero.

RESULTS

PSA and PAP in relation to clinical staging of radical prostatectomy patients. Cancer volume, and preoperative ambulatory PSA and PAP are presented in table 1 for each clinical stage of the 102 radical prostatectomies. There were no statistical differences in mean PSA, PAP or cancer volume between clinical stages A2 and B1. While PAP, as in the previous paper, failed to show significant differences between any successive clinical stages, mean PSA was highly significantly different between clinical stages B1 and B2 ($p < 0.004$) and significantly different between stages B3 and D1 ($p < 0.04$). Cancer volume was significantly different between clinical stages B1 and B2, B2 and B3, and B3 and D1. Average patient age in table 1 was 64 years.

PSA and PAP in relation to pathological staging of radical prostatectomy patients. Since clinical staging in comparison to actual cancer volumes can be imprecise[3, 8] we have examined the relationship of preoperative, ambulatory PSA and PAP to the actual cancer volumes found at radical prostatectomy. The data in table 2 show an excellent correlation between ambulatory serum PSA and increasing cancer volume but a poor correlation between cancer volume and serum PAP (with the exception of the largest cancers, 10 to 25 cc). These observations are confirmed when serum PSA and PAP are plotted against cancer volume for each of the 102 patients (figs. 1 and 2), in which the correlation coefficient for log PSA and log cancer volume is 0.70 but only 0.51 for log PAP versus log cancer volume. The 95 per cent limits for prediction of cancer volume from a given value of PSA or PAP can be determined from the upper and lower solid lines.

The degree of linear association between preoperative, ambulatory PSA and PAP with all of the histomorphological measurements made on the radical prostatectomy specimens is shown as Pearson correlation coefficients in table 3. A matrix of the bivariate scatter plot from which these values are derived is shown in figure 3.

Interrelationships among cancer volume, metastatic indexes and PSA. Of these 102 clinical stage A and B cancer patients 79 had neither invasion of the seminal vesicles nor lymph nodes, 11 had invasion of both, 10 showed invasion of the seminal vesicles alone and 2 were positive for lymph nodes in the absence of seminal vesicle invasion. Of the 79 cases with negative seminal vesicles and lymph nodes 31 showed some degree of complete capsular penetration into the periprostatic fat, 13 of which were more than 1 cm. Of the 102 patients the cancers in 48 were completely confined to the prostate.

We have shown previously that Gleason grade, capsular penetration, seminal vesicle invasion and lymph node metastases are all related to increasing cancer volume.[2, 3] In table 4 we present the mean cancer volume, mean linear extent of capsular penetration, percentage of patients with Gleason scores of 7 or more (that is contained Gleason grade 4 or 5 in more than 5 per cent of the cancer), the percentage of patients

TABLE 1. *Clinical stage, cancer volume, and preoperative ambulatory PSA and PAP in 102 consecutive radical prostatectomy patients*

Stage	No. Pts.	Cancer Vol.			PSA			PAP		
		Mean (cc)*	Range	P Value	Mean (ng./ml.)*	Range	P Value	Mean (ng./ml.)*	Range	P Value
A1	1	1.8	—		1.9	—		1.9	—	
A2	12	2.1 ± 1.0	0.05–12.4	>0.40 (not significant)	6.7 ± 2.6	0.4–32.1	>0.11 (not significant)	1.4 ± 0.2	0.6–2.9	>0.23 (not significant)
B1	31	2.3 ± 0.4	0.01–10.9	<0.001	10.0 ± 1.2	2.6–24.8	<0.004	1.6 ± 0.2	0.6–5.6	>0.13 (not significant)
B2	29	5.9 ± 0.9	0.42–25.5	<0.009	17.3 ± 2.4	2.4–56.0	>0.11 (not significant)	2.1 ± 0.4	0.3–8.2	>0.10 (not significant)
B3	16	10.7 ± 1.8	1.42–23.2	<0.04	29.9 ± 9.9	2.1–171	<0.04	3.6 ± 1.1	0.9–17.6	>0.17 (not significant)
D1†	13	17.3 ± 3.1	4.52–45.4		73.5 ± 22.5	12.8–266		4.9 ± 0.9	1.0–11.6	
Totals	102	6.5 ± 0.8	0.01–45.4		22.8 ± 3.9	0.4–266		2.6 ± 0.3	0.3–17.6	

* Mean ± 1 standard error.

† Original clinical stages were A2 (1 patient), B2 (7), B3 (4) and C (1).

TABLE 2. *Relationship of preoperative serum PSA and PAP to cancer volume in 102 consecutive radical prostatectomy patients*

Cancer Vol. (cc)	No. Pts.	PSA			PAP		
		Mean (ng./ml.)*	Range	P Value	Mean (ng./ml.)*	Range	P Value
0–1	19	5.7 ± 1.4	0.4–24.8		1.3 ± 0.1	0.6–3.2	
				<0.009			>0.08 (not significant)
>1–3	24	10.3 ± 1.3	1.2–24.5		1.6 ± 0.2	0.7–5.6	
				<0.006			>0.13 (not significant)
>3–10	37	16.2 ± 1.9	2.4–54.0		2.0 ± 0.3	0.3–7.8	
				<0.008			<0.003
>10–25	18	50.2 ± 13.8	6.4–239		5.2 ± 1.1	1.4–17.6	
				>0.07 (not significant)			=1 (not significant)
>25	4	117 ± 44.9	37.5–266		5.2 ± 0.6	3.7–6.8	

* Mean ± 1 standard error.

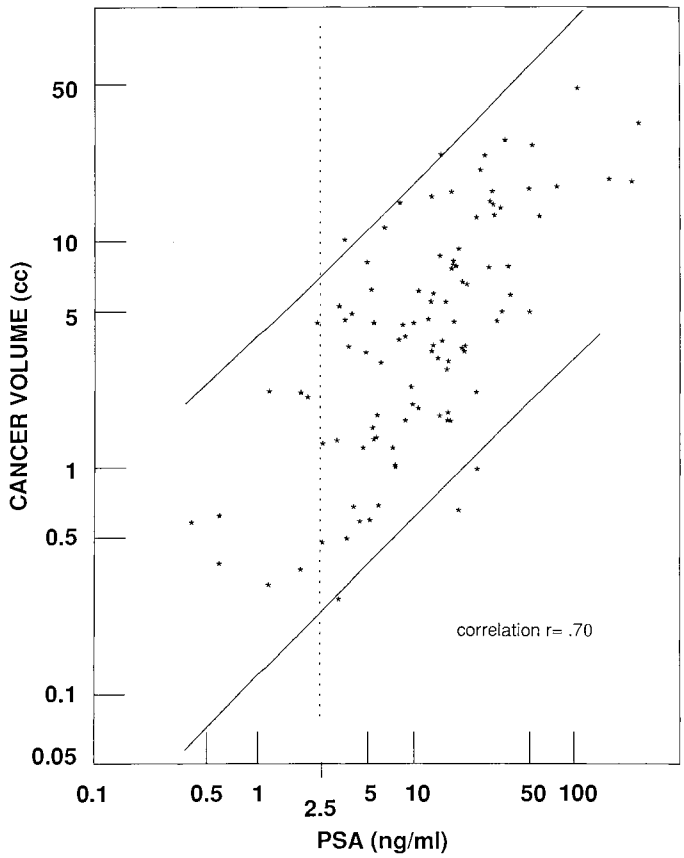

FIG. 1. Bivariate scatter plot of PSA against cancer volume + 0.25 for 102 patients (with axes on logarithmic scale). Correlation between log PSA and log cancer volume + 0.25 = 0.70. Ninety-five per cent prediction limits for prediction of cancer volume (+ 0.25) from given value of PSA for new patient are read from appropriate points on upper and lower solid lines. Vertical dotted line indicates upper limit of PSA for normal men (2.5 ng./ml.).[4]

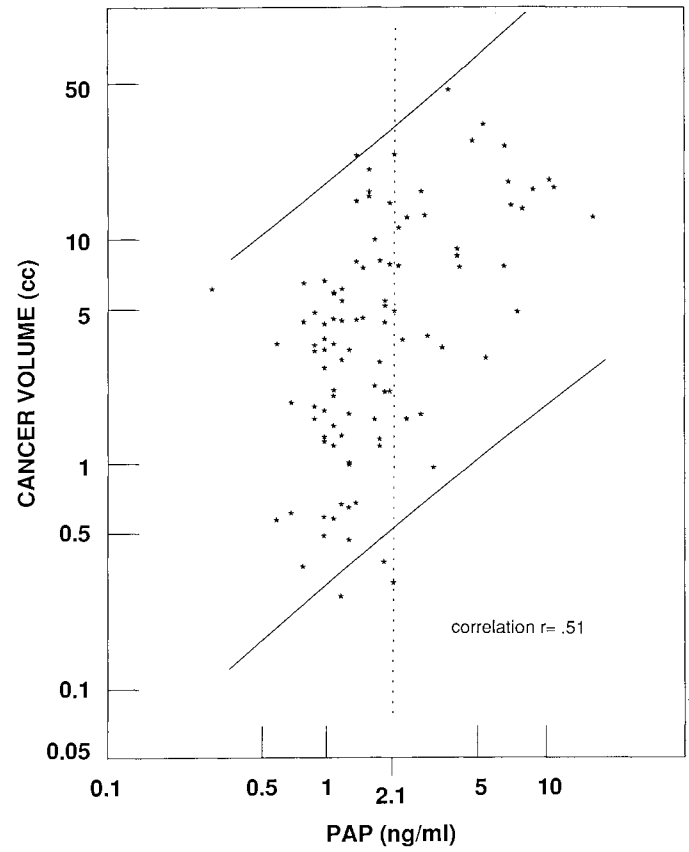

FIG. 2. Bivariate scatter plot of PAP against cancer volume + 0.25 for 102 patients (with axes on logarithmic scale). Correlation between log PAP and log cancer volume + 0.25 = 0.51. Ninety-five per cent prediction limits for prediction of cancer volume (+ 0.25) from given value of PAP for new patient are read from appropriate points on upper and lower solid lines. Vertical dotted line indicates upper limit of PAP for normal men (2.1 ng./ml.).[4]

TABLE 3. *Correlation coefficients describing relationships of log preoperative serum PSA and PAP concentrations, cancer volume and BPH to histomorphometric parameters in 102 radical prostatectomy specimens*

	Log Ca Vol.	Log PSA	Log PAP	Log BPH
Log Ca vol. (cc)	—	0.70	0.51	0.01
Log PSA (ng./ml.)	0.70	—	0.61	0.21
Log capsular penetration (cm.)	0.68	0.52	0.36	−0.02
Seminal vesicle invasion (+/−)	0.54	0.55	0.42	−0.09
% Gleason grade 4 or 5	0.45	0.41	0.27	0.07
Gleason score	0.45	0.36	0.09	0.07
Log prostate wt. (gm.)*	0.28	0.44	0.39	0.44
Log BPH ($cm.^2$)	0.01	0.21	0.15	—
Age (yrs.)	0.24	0.14	0.14	0.34

* Based on 97 specimens when weight was available.

who had capsular penetration into the periprostatic fat of more than 1 cm. and the percentage of patients with seminal vesicle invasion in relation to each clinical stage for the present group of 102 patients. Note that there is no difference in cancer volume between clinical stages A2 and B1 disease. The correlation coefficients between log cancer volume and all other histomorphometric parameters from the radical prostatectomy specimens, calculated from the bivariate scatter plots of figure 3, are shown in table 3. The best correlation is with log PSA, followed by log capsular penetration and seminal vesicle invasion, followed by correlations with Gleason grades and score. Thus, serum PSA correlates far better with cancer volume than Gleason grade. As expected, there is no significant relationship to prostate weight, age of the patient or presence of BPH.

Using multivariate linear regression analysis with log PSA as the dependent variable, in which all of these associations are

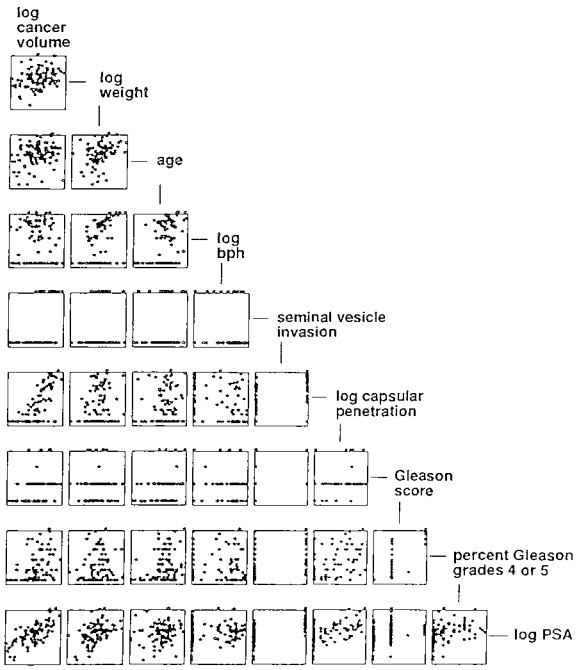

FIG. 3. Matrix of bivariate scatter plots of PSA, age and morphometric variables gives general indication of associations between variables taken 2 at time. For correlation coefficients see table 3. Note that some variables, such as seminal vesicle invasion and Gleason score, necessarily take limited number of values.

TABLE 4. *Relationship of cancer volume, Gleason score, capsular penetration and seminal vesicle invasion to clinical stage*

Stage	No. Pts.	Mean Ca Vol. (cc)*	Mean Capsular Penetration (cm.)*	Gleason Score ≧7†	Capsular Penetration >1 cm.†	Seminal Vesicle Invasion†
A1	1	1.8	0	0	0	0
A2	12	2.1 ± 1.0	0	42 (5)	0	0
B1	31	2.3 ± 0.4	0.47 ± 0.20	42 (13)	10 (3)	3 (1)
B2	29	5.9 ± 0.9	1.63 ± 0.44	72 (21)	41 (12)	14 (4)
B3	16	10.7 ± 1.8	2.44 ± 0.97	75 (12)	38 (6)	31 (5)
D1	13	17.3 ± 3.1	8.04 ± 1.33	100 (13)	100 (11)	85 (11)

* Mean ± 1 standard error.
† Per cent of patients with findings (number of patients).

considered simultaneously rather than 2 at a time as in the bivariate analyses, table 5 presents regression coefficients, t statistics, and p values from the multiple regression. Because 5 prostate weights were not obtained this analysis is based on 97 prostates. Logarithmic transformations of some variables were used when visual inspection of plots of PSA against those variables suggested an improved linear regression fit. The multiple R-square value was 0.66 and the statistically significant variables were cancer volume, prostate weight and presence of seminal vesicle invasion—a conclusion also supported by examination of a Cp plot[9] (data not shown). Of these variables cancer volume has the strongest association with PSA; linear regression analysis of log PSA plotted against log cancer volume alone achieves an R-square of 0.49, while the corresponding R-square values for prostate weight and seminal vesicle invasion are 0.19 and 0.31, respectively. If all variables, independent and dependent, are adjusted for cancer volume (by replacing them with their residuals after simple linear regression against log cancer volume), the R-square for the regression of log PSA against the remaining variables decreases to 0.27.

By comparison, multiple regression with log PAP as the dependent variable and the same independent variables yields a multiple R-square value of 0.41. Variables with 2-tailed p values of less than 0.05 were cancer volume, prostate weight, Gleason score and percentage of Gleason patterns 4 and 5.

TABLE 5. *Multiple regression analysis of preoperative log PSA as a dependent variable and selected independent variables in 97 radical prostatectomies*

Independent Variable	Coefficient	Standard Error	T Ratio	P Value*
Log cancer vol. (cc)	0.58	0.09	6.30	<0.001
Log prostate wt. (gm.)	0.66	0.21	3.15	0.002
Seminal vesicle invasion	0.81	0.25	3.20	0.002
% Gleason grade 4 and 5	0.004	0.0045	0.95	0.34
Age	−0.021	0.012	−1.84	0.07
Log BPH (cm.²)	0.10	0.061	1.69	0.09
Log capsular penetration (cm.)	−0.12	0.094	−1.32	0.19
Gleason score (2–10)	+0.062	0.16	0.38	0.70
Intercept	−0.11	1.38	−0.08	0.94

Multiple R-square = 0.66, 97 patients, F value = 20.92 on (8, 88) degrees of freedom. Residual standard error = 0.73.
* By 2-tailed t test of the null hypothesis that the appropriate regression coefficient vanishes.

TABLE 6. *Correlation of preoperative serum PSA concentration in 102 radical prostatectomy patients with pathological findings*

Pathological Parameter	PSA (ng./ml.)			
	<10	10–20	>20–50	>50
Gleason score ≧7*	40 (18)	71 (20)	90 (18)	89 (8)
Capsular penetration >1 cm.*	13 (6)	29 (8)	65 (13)	78 (7)
Seminal vesicle invasion*	2 (1)	11 (3)	45 (9)	89 (8)
Lymph node metastasis*	0	14 (4)	15 (3)	67 (6)
Mean Ca vol. (cc):	2.6	5.6	10.1	20.9
Standard error Ca vol.	±0.4	±0.9	±1.6	±3.8
P value	<0.002	<0.008	<0.005	
Total No. pts.	45	28	20	9

* Per cent of patients with findings (number of patients).

When the variables were adjusted for cancer volume as described previously the R-square decreased to 0.19.

How well does serum PSA and/or PAP predict the volume of prostate cancer? A linear regression of log cancer volume against log PSA and log PAP achieves a multiple R-square of 0.50 [equals $(0.71)^2$]. However, the coefficient of log PAP is not significantly different from zero (t = 1.5, 1-tailed p = 0.07) and after adjustment for PSA there is no association between cancer volume and PAP (r = 0.14).

A comparison of the results of the multivariate and bivariate analyses is instructive. The multiple R-square of 0.66 obtained in table 5 from the multiple linear regression of log PSA may be interpreted as the square correlation [$0.66 = (0.81)^2$] of the dependent variable log PSA with the fitted values of log PSA from the 8 independent variables (including log cancer volume). The bivariate analysis of log PSA against log cancer volume (as depicted in figure 3 and table 3) yields a correlation of 0.70 and, correspondingly, an R-square of $(0.70)^2 = 0.49$. Thus, the incorporation of 7 further independent variables in addition to cancer volume adds relatively little explanatory power to the regression (0.66 versus 0.49).

Value of preoperative serum PSA and PAP in determining pathological findings. Preoperative PSA as an indicator of Gleason score, capsular penetration greater than 1 cm., seminal vesicle invasion and metastases to pelvic lymph nodes using the Yang polyclonal radioimmunoassay is shown in table 6. With the data in this table the chances of a given patient with prostate cancer having certain pathological findings, especially pelvic lymph node metastases or seminal vesicle invasion, can be stated based upon the preoperative serum PSA level. Two important points should be made in regard to the PSA ranges used here: 1) the lowest PSA range, less than 10 ng./ml., is 4 times the normal range (0 to 2.5 ng./ml.) and still serves as an excellent cutoff to predict absence of seminal vesicle or lymph node involvement by cancer, and 2) each successive PSA range chosen in table 6 demonstrates not only a significant increase in the chance of important pathological parameters being positive but also describes a group of patients whose mean cancer

volume is roughly double that of the preceding group of patients (2.6 to 5.6 to 10.1 to 20.9 cc).

Similar data for PAP radioimmunoassay are shown in table 7. The fact that the normal range of serum PAP (2.1 ng./ml. or less) is inclusive of not only 73 per cent of the total patient group (74 of 102) but also 47 per cent (16 of 34) of the patients with seminal vesicle or lymph node invasion substantially limits its usefulness as a serum marker in prostate cancer. Moreover, note that the 3 abnormal ranges of PAP fail to distinguish increasing volumes of cancer significantly.

The ability of preoperative, ambulatory serum PSA to distinguish Gleason score, capsular penetration, seminal vesicle invasion and pelvic lymph node metastases is presented in table 8. Differences in preoperative PSA values for each of these pathological parameters are highly statistically significant.

Degree of capsular penetration into periprostatic fat. We have measured linearly, at 3 mm. intervals, the longitudinal extent of cancer penetration through the prostatic capsule into the periprostatic fat. The data in tables 9 and 10 suggest that serum PSA elevation, seminal vesicle invasion and pelvic lymph node metastases correlate only with cancer penetration greater than 1 cm. Moreover, there is no significant difference in cancer volume between patients with no capsular penetration and those with minimal capsular penetration of 1 cm. or less in extent (3.7 ± 0.7 versus 3.0 ± 0.4 cc, respectively). These are the first data to suggest that small areas of complete capsular penetration, totaling 1 cm. or less in longitudinal extent, may not be significant.

BPH. We have shown previously that BPH, in the absence of prostate cancer, elevates serum PSA at a rate of 0.3 ng./ml./gm. BPH tissue.[4] In the presence of prostate cancer, however, serum PSA is determined by the cancer and not the amount of BPH (tables 3 and 5).[4] Because of this apparent discrepancy, we have analyzed carefully the relationships among prostate cancer, BPH, prostate weight and preoperative serum PSA in these 102 patients.

Of 97 prostate weights available in these 102 radical prostatectomy specimens, the mean prostate weight was 41 gm. There was no relationship among increasing clinical stage, mean prostate weight or BPH (table 11) nor among increasing cancer volume, mean prostate weight or BPH (table 12). In fact, the data in both tables imply a negative correlation between volume of prostate cancer and BPH, especially in table 12, in which the measurements of cancer volume are much more accurate. There was, however, a good correlation between the amount of BPH and prostate weight. The mean prostate weight in 48 patients with BPH areas of 0 to 1 cm.^{2} was 35.2 ± 2.5 gm., while the prostate weight in 49 patients whose BPH was greater than 1 cm.^{2} was 46.8 ± 2.7 gm. ($p < 0.001$). Since it is important that serum PSA correlates with cancer volume (0.70) and not BPH (0.21), it is of interest also to evaluate BPH correlates in table 3 and figure 3. Log BPH correlates better, as might be expected, with the log of prostate weight (0.44) than anything else. A total of 45 patients had no BPH present in the specimen; if these are eliminated from the weight correlations the correlation coefficient increases from 0.44 to 0.59.

Preoperative serum PSA per cc prostate cancer at radical prostatectomy. The mean ambulatory preoperative serum PSA for the 102 patients was 22.8 ± 3.9, while the mean cancer volume found at radical prostatectomy was 6.5 ± 0.8 (table 1). The ratio of these 2 means is 3.5 ng./ml. per cc prostate cancer (median 3.4). The mean of the ratios was 9 ng./ml. per cc cancer, a much larger number caused by a small number of

TABLE 7. *Correlation of preoperative serum PAP concentration in 102 radical prostatectomy patients with pathological findings*

Pathological Parameter	PAP (ng./ml.)			
	≤2.1	>2.1–5.0	>5.0–10	>10
Gleason score ≧7*	55 (41)	75 (12)	89 (8)	100 (3)
Capsular penetration >1 cm.*	24 (18)	44 (7)	78 (7)	67 (2)
Seminal vesicle invasion*	15 (11)	13 (2)	63 (5)	100 (3)
Lymph node metastasis*	7 (5)	13 (2)	63 (5)	33 (1)
Mean Ca vol. (cc):	4.2	10.5	14.8	15.7
Standard error Ca vol.	±0.6	±2.8	±3.0	±1.4
P value		<0.02	>0.15†	>0.38†
Total No. pts.	74	16	9	3

* Per cent of patients with findings (number of patients).
† Not significant.

TABLE 8. *Ability of preoperative serum PSA concentration to distinguish Gleason score, capsular penetration, seminal vesicle invasion and pelvic lymph node metastases*

	No. Pts.	Mean PSA (ng./ml.)*	Range (ng./ml.)	P Value
Gleason score:				
≦6	38	9.3 ± 1.8	0.4–56.0	<0.001
≧7	64	30.8 ± 6.0	0.6–266	
Capsular penetration:				
0–1 cm.	68	11.8 ± 1.4	0.4–61.9	<0.001
>1 cm.	34	44.8 ± 10.5	3.6–266	
Seminal vesicle invasion:				
Neg.	81	12.1 ± 1.2	0.4–56.0	<0.001
Pos.	21	64.3 ± 15.6	8.0–266	
Pelvic lymph node metastasis:				
Neg.	88	15.5 ± 2.2	0.4–171	<0.005
Pos.	13	73.5 ± 22.5	12.8–266	

* Mean ± 1 standard error.

TABLE 9. *Relationship of preoperative serum PSA concentration to extent of capsular penetration in 102 radical prostatectomy patients*

Capsular Penetration (cm.)	No. Pts.	Mean PSA (ng./ml.)*	Range (ng./ml.)	P Value
Absent	49	11.9 ± 1.8	0.4–61.9	>0.40 (not significant)
>0–1	19	11.7 ± 1.8	2.4–33.4	<0.001
>1–2	9	28.5 ± 5.0	3.6–54.0	>0.06 (not significant)
>2	25	50.7 ± 14.0	5.0–266	
0–1	68	11.8 ± 1.4	0.4–61.9	<0.001
>1	34	44.8 ± 10.5	3.6–266	

* Mean ± 1 standard error.

TABLE 10. *Relationship of extent of capsular penetration to seminal vesicle invasion and pelvic lymph node metastasis*

Capsular Penetration (cm.)	No. Pts.	Seminal Vesicle Invasion*	Pelvic Lymph Node Metastasis*
Absent	49	2 (1)	0
>0–1	19	5 (1)	0
>1–2	9	33 (3)	11 (1)
>2	25	64 (16)	50 (12)
0–1	68	3 (2)	0
>1	34/33†	56 (19)	39 (13)

* Per cent of patients with findings (number of patients).
† 1 patient did not undergo lymphadenectomy.

TABLE 11. *Relationship of prostate weight and BPH to clinical stage prostate cancer*

Stage	Wt.			BPH		
	No. Pts.*	Mean Gm.†	P Value	No. Pts.	Mean (cm.^{2})†	P Value
A1	1	32		1	1.6	
A2	12	33 ± 7		12	1.7 ± 1.1	
			>0.17‡			>0.17‡
B1	28	43 ± 8		31	2.8 ± 0.5	
			>0.31‡			>0.27‡
B2	27	39 ± 3		29	2.4 ± 0.5	
			>0.33‡			=1‡
B3	16	41 ± 4		16	2.4 ± 0.8	
			>0.11‡			>0.38‡
D1	13	49 ± 5		13	2.1 ± 0.7	

* Prostate weight available in only 97 of 102 specimens.
† Mean ± 1 standard error.
‡ Not significant.

TABLE 12. *Relationship of prostate weight and amount of BPH to cancer volume in 102 radical prostatectomy specimens*

Ca Vol. (cc)	Wt.				BPH			
	No. Pts.*	Mean Gm.†	Range	P Value‡	No. Pts.	Mean ($cm.^2$)†	Range	P Value
0–1	17	33.2 ± 3.7	14.5–81.9		19	1.6 ± 0.5	0.0–5.9	
				>0.12				>0.09‡
>1 <3	22	39.4 ± 3.8	10.5–92.0		24	2.6 ± 0.6	0.0–10.0	
				>0.29				>0.26‡
>3 <10	36	42.1 ± 3.3	19.8–119		37	3.1 ± 0.5	0.0–10.0	
				>0.21				<0.05
>10 <25	18	46.6 ± 4.7	25.9–112		18	1.8 ± 0.6	0.0–10.0	
				>0.36				<0.02
>25	4	48.9 ± 4.9	33.5–60.2		4	0.3 ± 0.3	0.0–1.3	

* Prostate weight available in only 97 of 102 specimens.
† Mean ± 1 standard error.
‡ Not significant.

TABLE 13. *Summary of 9 patients with normal preoperative serum PSA concentrations (≦2.5 ng./ml.)*

Mean cc Ca vol. (range)*	1.15 ± 0.42 (0.05–4.0)
Seminal vesicle invasion (No. pts.)	0
Lymph node metastasis (No. pts.)	0
Capsular penetration (No. pts.):	
>0 cm.	1†
>1 cm.	0
No. pts. with postop. PSA = 0 ng./ml.‡ (mean followup 12 mos.)	9

* Mean ± 1 standard error.
† Only patient with any capsular penetration had clinical stage B2 disease, with 4 cc cancer volume.
‡ 0 ng./ml. = less than 0.3 ng./ml. (see Methods).

extreme values. From inspection of figure 1, the value of 3.5 ng./ml. per cc prostate cancer appears to be clinically correct. Thus, at least for the Yang assay, serum PSA elevation per gm. prostate cancer (3.5 ng./ml.) is 10 times that per gm. BPH (0.3 ng./ml.).

Radical prostatectomy patients with normal preoperative serum PSA and PAP. Of these 102 prostate cancer patients 9 (9 per cent) had normal preoperative serum PSA values (2.5 ng./ml. or less, table 13). Seven of these 9 patients had clinical stage A cancer when the serum PSA was obtained after transurethral resection of the prostate (see prior study[1]). The other 2 tumors were clinically staged as B2 (4 cc cancer, PSA 2.4 ng./ml.) and B3 (1.75 cc cancer, PSA 2.1 ng./ml.). The mean cancer volume for all 9 patients was 1.15 cc. Of these 9 patients 7 had cancers that were 100 per cent Gleason grade 3, while 2 had 20 per cent Gleason grades 4 and 5 (1 of whom had the stage B2, 4 cc cancer). All 9 cancers on pathological examination were localized to the prostate.

In contrast, 74 of the 102 patients (73 per cent) had normal preoperative serum PAP values (2.1 ng./ml. or less, table 7).

Followup serum PSA concentrations after radical prostatectomy. Of these 102 patients 97 have had multiple PSA determinations after radical prostatectomy. The average interval between prostatectomy and last followup PSA was 12 months, with a maximum followup PSA of 38 months.

Of the 97 patients 82 (85 per cent) have undetectable PSA (less than 0.3 ng./ml.) after radical prostatectomy. The distributions as to clinical stages, level of preoperative PSA, capsular penetration, seminal vesicle invasion and cancer volume are shown in table 14. All 82 patients had undetectable PSA in the serum within 3 weeks after radical prostatectomy.

All 9 patients who failed to show undetectable serum PSA levels at 3 weeks after radical prostatectomy never had a decrease to undetectable concentrations. However, 6 patients had decreases to undetectable levels for several months only to have detectable levels later and progressively increased levels unless adjunctive pelvic radiation therapy was instituted. Data on these 15 patients are presented in table 15.

Lastly, it is interesting to note how well combined seminal vesicle and pelvic lymph node tumor status serves as a predictor of postoperative serum PSA (table 16). Although the percentage of patients whose followup PSA is undetectable is not statistically different between those with or without seminal vesicle invasion, provided there is no pelvic lymph node metastasis, the cancer volumes, capsular penetration and preoperative PSA are different. These latter differences suggest that with a longer followup than our mean of 12 months there eventually may be a demonstrable statistical difference in post-prostatectomy serum PSA levels, and by inference clinical course, between patients with and without seminal vesicle invasion.

Margin-positive tissue planes. Of all the histopathological hallmarks of prostate cancer progression in radical prostatectomy specimens, evaluation of tissue margins is the most difficult to assess accurately. We have tried to evaluate margins at the apex and bladder neck by taking thin tangential sections after formalin fixation. If cancer is present on the inner surface of these tangential sections, or at the inked margin of the lateral capsule in any of the routine 3 mm. transverse sections in which the cancer is present in the periprostatic fat, we have called these positive margins. However, our routine of cutting these histological sections from the inner surface at the apex and bladder base does not necessarily mean cancer extended through to the opposite exposed surface signifying that cancer was left behind in the adjacent tissues. The disadvantage to these tangential sections can be reduced by taking serial sections parallel to the sagittal plane at the apex and bladder neck. We have not used this technique, however, because of our greater interest in accurately calculating cancer volumes using transverse sections. Nevertheless, using these thinly cut tangential sections at the apex and bladder neck as described, 14 of our patients without invasion of the seminal vesicles or lymph nodes would be considered to have positive margins at apex or base; an additional 6 showed cancer at the inked edge of the lateral capsule. These 20 margin-positive prostates had a mean cancer volume of 7.46 ± 1.3 cc, the mean preoperative PSA was 20 ± 2.9 ng./ml. and the mean preoperative PAP was 2.4 ± 0.4 ng./ml. Interestingly, we have followup PSA values for 19 of these 20 patients: 17 (89 per cent) have undetectable PSA concentrations with an average followup of 14 months. Although longer followup obviously is needed, these numbers would indicate that a positive surgical margin alone (by these histological definitions) may not be indicative of residual cancer tissue at these sites.

DISCUSSION

We presented a comprehensive histopathological and statistical analysis of 102 radical prostatectomy specimens in relationship to preoperative, ambulatory serum PSA and PAP. With bivariate analysis with calculation of Pearson correlation coefficients to measure direct linear association between any 2 variables as well as multivariate regression analysis to evaluate several independent variables simultaneously, we determined the relationship of PSA and PAP to all major determinants of prostate cancer progression: cancer volume, clinical stage,

Gleason grade and score, complete penetration of the cancer through the capsule into the periprostatic fat, seminal vesicle invasion and microscopic metastases to the pelvic lymph nodes.

The data in tables 1 to 3, 6 and 7, and figures 1 and 2 indicate the consistent disadvantages of even a sensitive PAP radioimmunoassay in comparison to PSA. Because acid phosphatase was the first tumor marker for any cancer, and has been used since 1938,[10] replacing PAP with PSA is an emotional, as well as an educational, issue. Nevertheless, our data combined with similar comparisons of these 2 enzymes in 230 patients with untreated prostate cancer in the preceding study[1] present what we believe to be justifiable reasons to replace what was the first serum marker for any epithelial cancer with what is now the first organ-specific tumor marker in cancer biology. In fact, the general belief among clinicians that PAP discriminated between intracapsular and extracapsular prostate cancer can be explained only by less than precise histological examinations of radical prostatectomy specimens combined with a general insensitivity of PAP to increasing cancer volume except at large tumor burdens (bone metastases), and perhaps by the lack of specificity of even immunologically specific PAP. Whatever the reasons, the general belief that a normal PAP excluded local extracapsular (or retroperitoneal) disease has been a major error in accurate staging of prostate cancer. The much greater sensitivity of PSA to the volume of prostate cancer now gives us an opportunity to diagnose surgical stage D1 disease with much greater accuracy and to follow this cancer during its long retroperitoneal history at a time when acid phosphatase, PAP and all imaging modalities appear to be normal.

Table 1 includes patients with clinical stages A2 to B3 cancers who have elevated serum levels of PAP. As discussed in the previous study, these patients often are believed to have advanced disease and have been placed in a separate category called stage D0. With reference to table 1, 1 of 12 stage A2, 6 of 31 stage B1, 7 of 29 stage B2 and 6 of 16 stage B3 cancers had elevated serum levels of PAP. Thus, 20 of 89 patients (22 per cent) would be classified as having stage D0 disease. However, all 20 patients had benign pelvic lymph nodes at surgical staging and only 3 showed seminal vesicle invasion. We conclude that elevations of serum PAP, at least when determined by a sensitive radioimmunoassay, probably are caused by intracapsular prostate cancer and cannot be used to define a separate D0 clinical category.

Tables 2, 3, 5 and 6, and figures 1 and 3 confirm our previous observations that the serum level of PSA, at least by the polyclonal Yang assay is proportional to the volume of intracapsular prostate cancer,[4] an observation that we believe also is unique among human epithelial cancers. The data in table 6 illustrate the usefulness of preoperative, ambulatory serum

TABLE 14. *Data on followup serum PSA concentration in 97 patients after radical prostatectomy*

Pt. Category	Last Postop. PSA 0 ng./ml.* No. Pts./Total (%)	Mean Followup (mos.)
A1	1/1 (100)	18
A2	10/10 (100)	9
B1	30/30 (100)	13
B2	25/27 (93)	11
B3	11/16 (69)	11
D1†	5/13 (38)	12
Preop. PSA:		
<10	41/42 (98)	10
10–20	21/27 (78)	13
>20–50	16/19 (84)	14
>50	4/9 (44)	11
Capsular penetration (cm.):		
0	43/46 (93)	12
0–1	61/65 (94)	12
>1	21/32 (66)	11
Seminal vesicles:		
Neg.	69/76 (91)	12
Pos.	13/21 (62)	12
Ca vol. (cc):		
≦1	18/18 (100)	11
>1–3	20/22 (91)	14
>3–10	31/35 (89)	11
>10–25	11/18 (61)	11
>25	2/4 (50)	12
Totals	82/97 (85)	12‡

* 0 ng./ml. = less than 0.3 ng./ml. (see Methods).

† Of the 5 stage D1 cancer patients who have postoperative PSA values of 0 ng./ml., 4 have received postoperative pelvic irradiation and 1 has had bilateral orchiectomy.

‡ Maximum followup 38 months.

TABLE 16. *Combined seminal vesicle and lymph node status as predictor of postoperative serum PSA concentration after radical prostatectomy*

	Seminal Vesicles/Lymph Nodes		
	Neg./Neg.	Pos./Neg.	Pos./Pos.*
No. pts.	78	10	11
Mean preop. PSA (ng./ml.)†	12.0 ± 1.2	43.0 ± 14.2	83.6 ± 25.4
Mean Ca vol. (cc)†	4.0 ± 0.5	12.2 ± 3.0	18.4 ± 3.5
Mean capsular penetration (cm.)†	0.6 ± 0.2	4.8 ± 1.3	8.8 ± 1.5
% with postop. PSA = 0.0†, ‡	92 ± 3	80 ± 13	45 ± 15
P value	>0.18 (not significant)	<0.04	

* Data exclude the only 2 patients with negative seminal vesicles and positive lymph nodes.

† Mean ± 1 standard error.

‡ All patients had postoperative PSA values except 4 of the 78 in the Neg./Neg. column.

TABLE 15. *Summary of 15 patients with detectable serum PSA levels after radical prostatectomy*

Pt. No.	Stage	Gleason Score	Ca Vol. (cc)	Capsular Penetration (cm.)	Seminal Vesicle Status	Surgical Margin	PSA (ng./ml.) Preop.	Nadir	Latest	Mos. Postop.	Adjunct Therapy
1	B2	7	1.4	0.8	−	−	14.4	0.0*	0.5	27	Radiotherapy
2	B2	7	12.1	10.0	−	+	24.5	0.4	0.4	12	Radiotherapy
3	B3	6	2.9	0	−	−	4.9	0.0	1.9	13	—
4	B3	7	5.0	0	−	+	12.6	0.0	5.5	12	—
5	B3	7	23.2	0	−	−	14.7	0.5	0.5	7	—
6	B3	7	22.9	11.0	+	+	27.9	1.5	1.5	9	—
7	B3	7	18.1	11.5	+	+	171	68.0	135	6	—
8	D1	9	15.1	14.0	+	+	12.8	1.3	12.1	12	—
9	D1	9	15.8	4.5	−	+	17.1	0.0	35.0	20	—
10	D1	7	7.3	3.5	−	−	18.3	13.9	13.9	7	Radiotherapy
11	D1	7	6.2	3.5	+	−	20.1	0.0	3.1	11	Diethylstilbestrol
12	D1	7	4.5	2.0	+	−	54.0	0.0	0.9	18	—
13	D1	7	45.4	8.5	+	+	108	0.7	4.5	21	Radiotherapy
14	D1	7	17.6	4.5	+	+	239	69.6	127	4	—
15	D1	7	32.0	18.0	+	+	266	1.0	1.2	12	Radiotherapy
Mean values		7.2	15.3	6.1			67.0	10.5	19.0	13	

* 0 ng./ml. = less than 0.3 ng./ml. (see Methods).

PSA to detect sequential doubling of cancer volumes and, thereby, strongly suggest the presence or absence of seminal vesicle or pelvic lymph node metastases. If the PSA is less than 10 ng./ml. by the Yang assay we believe that we can predict confidently a minimal chance of seminal vesicle or lymph node invasion. On the other hand, a PSA before radical prostatectomy of more than 50 ng./ml. carries a 90 per cent chance of seminal vesicle invasion and 2 of 3 chances that the pelvic lymph nodes will be positive. Serum PSA values between 10 and 50 ng./ml. show a proportional increase in seminal vesicle invasion and pelvic lymph node metastases. Since capsular penetration occurs early in the natural history of prostate cancer, even a serum PSA of less than 10 ng./ml. carries a small risk of substantial penetration of greater than 1 cm. (13 per cent); these 6 cases with capsular penetration of greater than 1 cm. were among the largest cancers in the 45 patients with preoperative PSA levels of less than 10 ng./ml. (mean volume 8.6 cc) and included the patient with seminal vesical invasion. However, a PSA of greater than 50 ng./ml. has a 78 per cent chance of greater than 1 cm. capsular penetration. Thus, a serum PSA before radical prostatectomy is a powerful tool to estimate the volume of cancer within the prostate, which in turn determines the degree of extracapsular extension.[2,3]

One of us (J. E. M.) has long believed that small amounts of capsular penetration (1 cm. or less) may not be biologically significant in terms of preventing a potential cure by radical prostatectomy. Although longer followup with frequent determinations of post-radical prostatectomy serum PSA ultimately will show whether capsular penetration (and what degree) in the absence of seminal vesicle and lymph node metastases is significant, tables 9 and 10 indicate that the mean PSA concentration, incidence of seminal vesicle invasion and pelvic lymph node metastases in our patients with 1 cm. or less of capsular penetration is no different than those without any capsular penetration. On the other hand, patients with greater than 1 cm. capsular penetration show substantial increases in mean PSA (table 9, $p < 0.001$), and a much higher incidence of seminal vesicle and pelvic lymph node invasion (table 10). This constitutes our first evidence that 1 cm. or less of total capsular penetration may not portend ultimate metastatic disease.

Tables 3 and 5 show that serum PSA, in the presence of cancer and BPH in a radical prostatectomy specimen, reflects the volume of cancer, not the volume of BPH. However, in the absence of cancer, BPH strongly influences serum PSA at a rate of 0.3 ng./ml./gm. BPH.[4] We have expanded our original BPH series from 73 transurethral resections to 94 in which every tissue chip was embedded to exclude cancer in these prostates that were benign on digital rectal examination. The mean weight of the resected tissue was 35 ± 32 gm. (standard deviation), with a range of 2 to 180 gm. (median 26 gm.). The mean preoperative serum PSA was 9.0 ± 8.4 ng./ml. (standard deviation), range 0.4 to 38 (median 5.7 ng./ml.). The ratio of these 2 means for this larger group of patients is 0.26 ng./ml./gm. BPH. Repeat PSA serum levels 3 or more weeks after transurethral resection of the prostate for 63 of these 94 cases were 3.4 ± 5.5 ng./ml., with a range of 0 to 26 (median 1.2 ng./ml.). Thus, we again confirm that BPH in the absence of prostate cancer increases serum PSA at a rate of about 0.3 ng./ml./gm. BPH tissue. Tables 11 and 12 indicate that there is no significant relationship between successively increasing volumes of prostate cancer and prostate weight whether the cancer volume is estimated by clinical stage (table 11) or actually measured by determining cancer volume in pathological specimens (table 12). In fact, tables 11 and 12 actually suggest a negative correlation between volume of prostate cancer and BPH. However, as would be expected, prostate weight was related to the amount of BPH (table 3 and text).

Table 1 shows that the mean PSA in these 102 patients was 22.8 ± 3.9 ng./ml. serum in the presence of a mean cancer volume of 6.5 ± 0.8 cc, that is the elevation in serum PSA averages 3.5 ng./ml./gm. cancer, a value at least 10 times higher than the elevation caused by BPH. This observation may be at least partly the explanation why serum PSA in the presence of cancer and BPH in our radical prostatectomies is determined primarily by the cancer. The value of 3.5 ng./ml./gm. cancer in these 102 radical prostatectomies is not weighted by larger cancers with metastases because the 36 patients who had either positive lymph nodes, positive seminal vesicles or capsular penetration of more than 1 cm. had a mean PSA of 44.6 ng./ml., with a mean cancer volume of 12.6 cc (3.5 ng./ml./gm. cancer). The 66 cancers that were totally organ confined or had less than 1 cm. capsular penetration had a mean PSA of 10.98 ng./ml., with a mean cancer volume of 3.1 cc (3.5 ng./ml./gm. cancer).

The actual mechanism whereby intracapsular prostate cancer and BPH elevate serum PSA is unknown, nor do we know how PSA reaches the blood in men with normal prostates without cancer or BPH. We do know that normal seminal fluid contains about 700 μg./ml. (2 standard deviations is 200 to 3,020 μg./ml.) of PSA,[11] a concentration 1 million times that in the serum. Our observations that prostate cancer, gram for gram, increases serum PSA 10 times as much as BPH need an explanation. It is unlikely that intracapsular prostate cancer per se contributes more to the elevation of serum PSA than normal or BPH prostatic epithelial cells. For example, it is known that there is less acid phosphatase activity per gram tissue in prostate cancer than is present in normal or hyperplastic glands,[12] an observation likely to be true of PSA as well. This observation is in keeping with the concept in general cancer biology that rarely does the cancer cell do anything as well as the normal parenchymal cell from which it arose. Nevertheless, it is interesting that such a unique and highly conserved protein in normal prostatic epithelial cells continues to be expressed so strongly in malignant cells. This expression of PSA by extraprostatic cancer clearly is responsible for the progressive relationship between serum PSA and increasing volumes of extraprostatic cancer.

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