MEDICAL GRAND ROUNDS

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT DALLAS

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CARCINOMA OF THE PROSTATE

CONTROVERSIES AND DILEMMAS CONFRONTING THE INTERNIST.

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Adenocarcinoma of the prostate is the second most common neoplasm in men in the United States. There is a projected incidence of over 80,000 new cases in 1985 and 25,000 men are expected to die of this tumor this year (1). Recent advances in the characterization of the natural history of this tumor, availability of a variety of laboratory tests and new staging procedures, important advances in surgical techniques and a new understanding of potential hormonal manipulative measures in therapy have refocused interest in this tumor. In spite of the magnitude of the problem and these recent advances, it is noteworthy that the urologic experts in this arena emphasize the significant "dilemma" in identifying and selecting the appropriate therapeutic approach in the management of patients with carcinoma of the prostate (2-8).

Epidemiology of Prostate Carcinoma

In spite of the incidence of adenocarcinoma of the prostate, the relevant risk factors for this tumor are poorly delineated. Geographic differences in incidence and mortality are clear; low rates are seen in the Orient, intermediate in South America and South Europe, and high rates in North American and Northern Europe (9).

The most dramatic change in the epidemiologic pattern in the United States has been the remarkable increase in prostate cancer in blacks. These rates are now twice that of whites in the United States (10, 11).

U.S. Age-Adjusted Prostate Cancer Mortality by Decade, 1950-1979*

	1950-59	1960-69	1970-79
U.S. white males	20.7	19.7	20.3
U.S. black males	26.5	31.9	34.3

*Rate per 100,000 man-years, 1970 U.S. standard.

Although adenocarcinoma of the prostate is clearly androgen-dependent, the role of the hormonal milieu is not entirely understood. It is known that eunuchs and young men castrated post puberty do not acquire the disease. Familial factors have been examined, and it is of interest that brothers of patients identified with prostate cancer prior to the age of 62 have a fourfold likelihood of developing the same lesion, when compared to the general population (12). In pursuit of the "metabolic epidemiology" of prostate cancer, the index cases and their brothers had significantly lower mean plasma testosterone levels, high clearance rates of testosterone, and a high conversion ratio of testosterone to estradiol when compared to matched controls of similar age.

Although an age-associated incidence appears evident in the United States, epidemiologic studies now stress that this disease is not an inevitable consequence of aging (13). Wynder et al. (13) have further demonstrated that diets high in fat appear important in some of the geographic features of the incidence of prostate cancer.

Evidence Supporting a Dietary Hypothesis for the Cause of Prostatic Cancer

1. A strong positive correlation between dietary fat consumption and prostatic cancer incidence worldwide.
2. Breast and prostatic cancer rates are closely correlated in most countries. Both are most common in northern Europe and the United States, where fat consumption is highest.
3. Prostatic cancer rates are highest in U.S. counties where fat consumption is also high.
4. Time trends within Japan: Fat intake and prostatic cancer have increased steadily with time since 1950.

In support of this, studies in Japan demonstrate that "Western food habits" are clearly implicated when a matched-pair analysis of cases was examined (14). Similar studies in the United States have examined blacks and noted risk enhancement with increased fat (total and saturated) intake as well as with increased intake of vitamin A during the age period of 30-49 years (15).

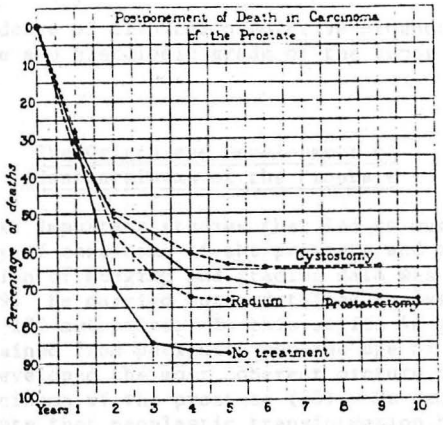
Natural History

The "natural history" of the neoplasm is the expected sequence of clinical laboratory findings during the untreated course of the disease. Since the incidence of acinar carcinoma of the prostate is age-related, as the potential host grows older, other diseases of the aged shorten his survival and may limit the full biologic expression of his prostate cancer.

A classic enigma that served to confuse the clinical approach to the patient with carcinoma of the prostate resulted from studies such as the classic of Franks (16), who emphasized the age-related incidence of this tumor and demonstrated that greater than 50% of aged men had the lesion at autopsy, although they were without symptoms. This incidence was recently reaffirmed in studies from Houston (17) that identified a nearly 50% incidence of carcinoma of the prostate in men over the age of 70. These studies of Franks led to the concept that carcinoma of the prostate was expressed in most patients as a "latent" tumor. The generated concept from that was that in some mysterious way two different biologic fates were seen with carcinoma of the prostate: one that was benign and latent and the other expressed as a more classic neoplastic disease with progressive involvement and the potential for death. These observations led to the general concept that prostate cancer was one with a highly varied and unpredictable "natural history".

This concept of a highly variable natural history, still current today, is not supported by the examination of surveys of large patient groups. For instance, Bumpus (18) reported on 1,000 patients with histologically proven adenocarcinomas of the prostate seen at the Mayo Clinic prior to 1925. These data, antedating elegant staging and histologic grading, provided most of what is known about the clinical presentation of this disease in the symptomatic state. Thus, 65% of the patients seen presented with obstructive symptoms, primarily frequency and difficulty with urination, and 16% of the patients presented with symptoms consistent with metastatic disease, primarily pain in the back and thighs. Of interest is that no patient presented with gross hematuria. In the course of followup, 243 (24%) had defined metastatic disease. Of this group, 44% had metastatic involvement of the lymphatics easily related to the rich lymphatic bed in the prostate with drainage to the internal and external iliac node chains. The serial evaluation demonstrated that lymph node metastases were the earliest and most frequent site. The second most frequent site was to bone and 25% of the patients had that evident by roentgenogramic examination. Examination of one subset of patients with pulmonary involvement (1.2%) demonstrated not only the uncommonness of that site but that all had spine or pelvic bone involvement. Perhaps as the first DRG recommendation in the United States, Dr. Bumpus suggested that chest X-rays were unnecessary except for those patients who had bone involvement!

Since any "therapeutic" program should improve on the projected clinical future of the patient, the expected course and the potential for postponement of death were examined by Bumpus (18). In 485 cases (48.5%) no treatment was given and the average duration of disease from initial symptoms to death was 31 months. When metastatic disease was evident at presentation the medial survival was less than 9 months (2/3 of the patients were dead at 9 months).



Postponement of death in carcinoma of the prostate after various procedures.

Data from a variety of clinical centers (refs. 19-24) suggest that the natural history of prostate cancer is not "variable". Although the growth rate of the tumor appears to be low, some degree of clinical predictability could repeatedly be identified based upon such criteria as histologic grade and tumor size. Thus, in 1956 Pool and Thompson (19) reviewed 1560 patients at the Mayo Clinic between the years 1926 and 1946. Each had been originally identified by a transurethral prostatic resection. They noted that there was a progressive increase in the 5-year survival and that overall survival could be related to the histologic grade of the tumor.

Mayo Clinic Data on Survival in Prostate Carcinoma (1926-1946)

	% Survival	
Grade	5 yr	10 yr
I	59.5	40
II	34.1	9.8
III	16.2	3.1
IV	5.6	0

Similarly, Barnes and Ninan (20) provided a survival comparison between patients with focal lesions and those with diffuse lesions of similar stage. Their 10-year survival was 76% for focal lesions and 45% for diffuse lesions.

Thus, the evidence of clinical predictive prognostic potential based upon the size and histologic grade of the tumor has slowly evolved.

The Origin and Development of Adenocarcinoma of the Prostate

One of the most important studies that led to our contemporary view of the biology of carcinoma of the prostate and allowed an appropriate interpretation of staging and grading data was generated by Dr. John McNeal in 1969. He carried out a detailed analysis of prostate glands obtained in 134 autopsies. In this series 45 glands contained carcinoma, all obtained from patients over the age of 40. His careful analytic studies developed the most coherent picture of the origin and development of carcinoma of the prostate (25). He demonstrated that the previous concepts that neoplastic transformation had a predilection for the posterior lobe or the supracapsular areas of the prostate were

incorrect. A clarification of this latter point is very nicely expressed in his subsequent monograph (26) where he demonstrated that presuming a cube 10 cm on each side approximately 50% of the volume is found within 1 cm of the surface, or for the prostate, the capsule. Thus, randomly distributed events would be expected in 50% of the cases to occur not more than 10% of the distance from its surface; hence, the misconception of the subcapsular site of origin for prostatic cancer in the older literature. A second finding from these studies was the evidence that carcinoma was selectively recognized from active glandular epithelium rather than from atrophic glands, and he was able to demonstrate a distinctive premalignant pattern of changes accompanying the origin of the cancer. The most important findings that were pivotal in further understanding the biology of prostate cancer related to his evidence that the volume distribution data suggested that there were not in fact two types of prostate cancer with different biologic potential but rather a single cancer having a slow growth rate with logarithmic growth curve. He demonstrated that the development of the carcinoma followed predictable patterns that resulted in early involvement of the capsule and that tumor size and growth were associated with an important loss of differentiation, and this change in tumor size and differentiation was further associated with the potential for penetration of the capsule and expansion beyond the prostate gland (25, 26). In his initial proposals he felt that the capacity for distant metastases was largely limited to larger carcinomas and, as has been amply proven, the penetration of the capsule of the gland was the most important predisposing factor to metastases.

The concept of a loss of differentiation with growth was the key concept upon which the biologic history of prostate cancer was expanded by Dr. McNeal (25, 26) and developed in the clinical setting by Thomas Stamey (3). These concepts that the differentiation of the gland correlates strongly with tumor volume in the prostate and that the poorly differentiated tumors, which are associated with a shortened life expectancy, are consistently of larger size were supported by the very extensive studies of Gleason (27) from the careful analysis of 2,911 cases examined in the VA Cooperative Urologic Research Group Program. The proposal that tumor volume increases along a continuum and that along that continuum a progressive dedifferentiation, or loss of differentiation, relates to that increasing volume and increasing malignant characteristic tumor has not been a consistent feature of other tumors. Important support for that concept was recently generated by Brawn (28) in the examination of 54 patients with prostate cancer who had more than one transurethral resection of the prostate over a period that ranged between 3 and 11 years. Approximately 80% of these tumors demonstrated loss of differentiation at the time of the second examination.

McNeal (26) has brought together the data supporting a relatively low growth rate for prostate cancer with a relatively long doubling time. He suggests that these tumors best fit the pattern of a plateau phase of the growth curve without significant changes in growth rate with time or volume increase. As he has pointed out, such a curve would explain the great excess of very small prostate cancers. For instance, if a tumor requires approximately 30 mass doublings to reach a volume of one cubic

centimeter and is responsible for death at approximately 40 mass doublings, then 75% of the tumors at the time of autopsy would be less than one cubic centimeter in volume. He views the evidence as supporting this tumor to be a lesion with a relatively unvarying, predictable natural history and with a strong correlation between tumor volume, differentiation and aggressiveness. Aggressiveness related to the degree of differentiation then becomes a focal point at which metastases occur. Unfortunately, at the present time the temporal or biologic point at which the change in mass and differentiation variables result in metastases is not known.

From his studies and the recent supporting data, McNeal has projected the following scenario (26). During the early period of growth of the tumor, differentiation is present and it can be estimated that it would take 10 to 15 years to reach a size of approximately 0.5 grams. Growth continues with a selective extension, perhaps because of the predilection to perineural space involvement toward the capsule, and it masses between 0.5 and 2 grams. The tumors often have a wedge-like contour with the base against the capsule. Then, through the next two mass doublings the dominant direction of growth appears to be laterally and the evidence supports the fact that differentiation decreases significantly during this time. When the mass reaches approximately 4 grams in size the carcinoma begins to penetrate deeply into the prostate, often extending across the midline. By the next doubling, when the tumor achieves a mass of approximately 8 grams, areas of poor differentiation have been confirmed and it is the postulate that this is the point of the earliest appearance of lymph node metastases. Certainly it is at this time that microscopic foci of cancer that are not connected to the parent mass may be seen. McNeal has postulated a series of subsequent events associated with serial doublings from that point that involve the evident extra-prostatic extension, invasion into the central zone and into the seminal vesicles, as well as subsequent bony metastases. The observations suggest that the increase in tumor volume with parallel loss of differentiation form a pattern of a continuum that is associated with gradually increasing invasiveness. This change in tumor volume, the loss of differentiation, and invasiveness appear to be closely linked. The careful dissection of material over the past decade has thus provided the clearest understanding of the natural history of prostate cancer and has made meaningful the previous attempts at developing clinical stage and grades of cancer into a workable schema for therapeutic interdiction.

Growth Rate Projections

Time required to 1 cm. diameter nodule (10^9 cells)
(Approximately 30 doublings)

Presumed:	Doubling Interval	Time Required
- cell of	1 month	2 yrs
10μ	3 months	8 yrs
diameter	6 months	16 yrs

Staging

Critical to a characterization of the clinical status of patients is the delineation of the extent of disease or "staging". Whitmore (29) developed the first and most widely used staging classification for prostatic carcinoma. Whitmore's classification has been often called the American Urologic System (30), and although it is a highly popular system the so-called TNM (Tumor-Nodes-Metastases) System developed by the International Union Against Cancer is now considered the preferable staging system.

Classification of Adenocarcinoma of Prostate

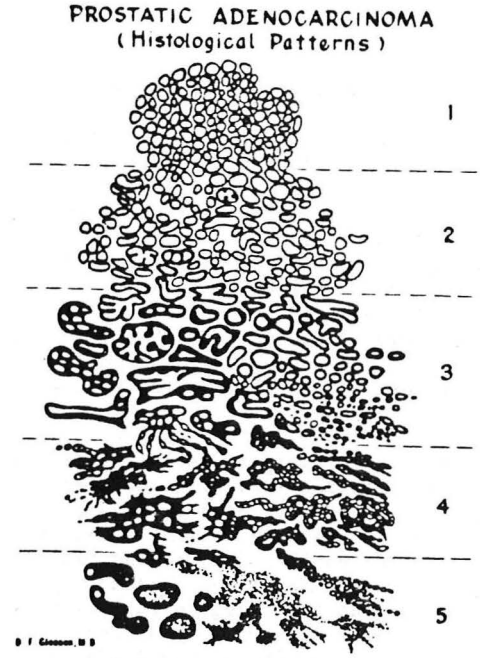
American Urological Staging System		TNM**
Stage A:	Clinically undetectable Incidental finding	TO: No tumor present
A_1:	Focal (3 or less foci; must be well differentiated)	Tla: < 3 high power fields by micro
A_2:	Diffuse (> foci or "high grade" histology)	1b: > 3 high power fields of tumor
Stage B:	Confined within capsule	T2: Confined within capsule
B_1:	Discrete nodule < 1.5 cm	a: Nodule < 1.5 cm
B_2:	Large nodule or one lobe	b: Nodule > 1.5 cm or nodule or induration both lobes
B_3:	Bilobar involvement	
Stage C:	Invades periprostatic area (local extension)	T3: Tumor beyond capsule
C_1	Normal seminal vesicles; < 70 g	a: Periprostatic or one seminal vesicle
C_2:	Involved seminal vesicles; > 70 g	b: Both seminal vesicles; or tumor > 6 cm
Stage D:	Metastatic disease	T4: Fixed or involving near structures
D_1:	Pelvic lymph nodes	
D_2:	Other metastatic disease	
		N: Nodal involvement
		N1: One homolateral
		N2: Contralateral or bilateral
		N3: Pelvic mass with free space between it and primary
		M: Distant metastasis Specify _____

**Manual for Staging of Cancer of Amer. Joint Comm. on Cancer, 2d ed., OH Beahrs, MH Myers. Lippincott, Philadelphia, 1983, pp. 159-164.

Grading

The grading of neoplasms has largely been on a histologic basis and, as noted above, studies such as Pool and Thompson (19) show important correlations between the histologic pattern and survival. Three histologic features have been used in diagnosis: 1.) cellular atypia, 2.) architectural disturbances, defined as a loss of the regular lobular pattern, and 3.) invasion (32). Clearly, invasion of the vascular bed, the capsule or the seminal vesicles adversely affect survival. By contrast, perineural invasion, a finding in nearly 90% of cancers, has no prognostic significance.

The most important advance in the clinical interpretation of adenocarcinoma of the prostate was developed by Dr. Donald Gleason (27) on the basis of a careful examination of 2,911 patients who were part of the Veterans Administration Cooperative Urologic Research Group studies (VACURG); these studies, begun in 1960 as controlled, randomized, prospective comparisons of a variety of treatments for cancer of the prostate, resulted in some of the most extensive data on therapeutic trials available. From these cases and the related data Gleason developed a histologic classification of prostate cancer based only upon the degree of glandular differentiation and the general growth pattern of the tumor in relationship to the prostatic stroma when reviewed under low power magnification. He was able to demonstrate that this classification showed a very close correlation with mortality rates. The five patterns that he depicted are shown:



Simplified drawing of histologic patterns, emphasizing degree of glandular differentiation and relation to stroma. All black in the drawing represents tumor tissue and glands with all cytologic detail obscured except in right side of pattern 4 where tiny open structures are intended to suggest the "hypernephroid" pattern.

The specific criteria of these five histologic patterns are defined as follows:

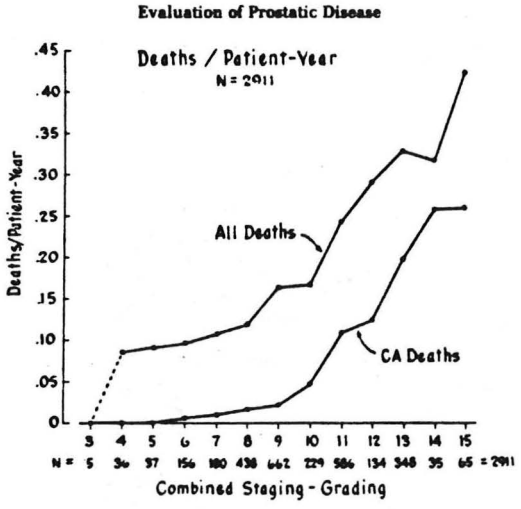
Histologic patterns of adenocarcinoma of the prostate

Pattern	Margins of Tumor Areas	Gland Pattern	Gland Size	Gland Distribution	Stromal Invasion
1	Well defined	Single, separate, round	Medium	Closely packed	Minimal, expansile
2	Less definite	Single, separate, rounded, but more variable	Medium	Spaced up to one gland diameter, average	Mild, in larger stromal planes
3 or	Poorly defined	Single, separate, more irregular	Small, medium, or large	Spaced more than one gland diameter, rarely packed	Moderate, in larger or smaller stromal planes
3	Poorly defined	Rounded masses of cribriform or papillary epithelium	Medium or large	Rounded masses with smooth sharp edges	Expansile masses
4	Ragged infiltrating	Fused glandular masses or "hypernephroid"	Small	Fused in ragged masses	Marked, through smaller planes
5 or	Ragged, infiltrating	Almost absent, few tiny glands or signet ring cells	Small	Ragged anaplastic masses of epithelium	Severe, between stromal fibers or destructive
5	Poorly defined	Few small lumina in rounded masses of solid epithelium central necrosis?	Small	Rounded masses and cords with smooth, sharp edges	Expansile masses

As expected, many of the tumors examined had more than one histologic pattern within it. Gleason analyzed the classic pathologist credo that "a tumor is as bad as its worst part" (27). His analysis demonstrated that although the cancer mortality rates did correlate closely with the "worst" pattern, surprisingly the correlation with the "best" pattern appeared stronger. From his analysis he concluded that at least for cancer of the prostate the biologic malignancy of the tumor was more closely related to the average histologic pattern than to either its worst or best patterns (27). In an attempt to avoid fractional grades to describe this event, he developed his first step of his grading system, now termed the Gleason Grading System, that was the added numerical result of that worst and that best recognized grade in any tumor. Thus, his final histologic scores ranged between 2 and 10.

Gleason integrated the clinical staging into his grading system. His analysis, for instance, confirmed that patients with stage C disease who had an elevated prostatic acid phosphatase in the absence of demonstrable metastases were at higher risk for death than those same patients with a normal acid phosphatase. Since the death rates associated with the histologic pattern scores showed some overlapping of death rates between the clinical stages, he combined the histologic grading and clinical staging. He did this by adding the initial clinical stage of the tumor to the final histologic score. To achieve this, he added 1 for stage A, 2 for stage B, 3 for stage C and 5 for stage D. Thus, the final Gleason score was a number based upon the addition of the best and worst of the histologic grading plus the clinical stage at initial diagnosis. The range, therefore, of Gleason stage was between 3 and 15.

When he plotted these relationships:

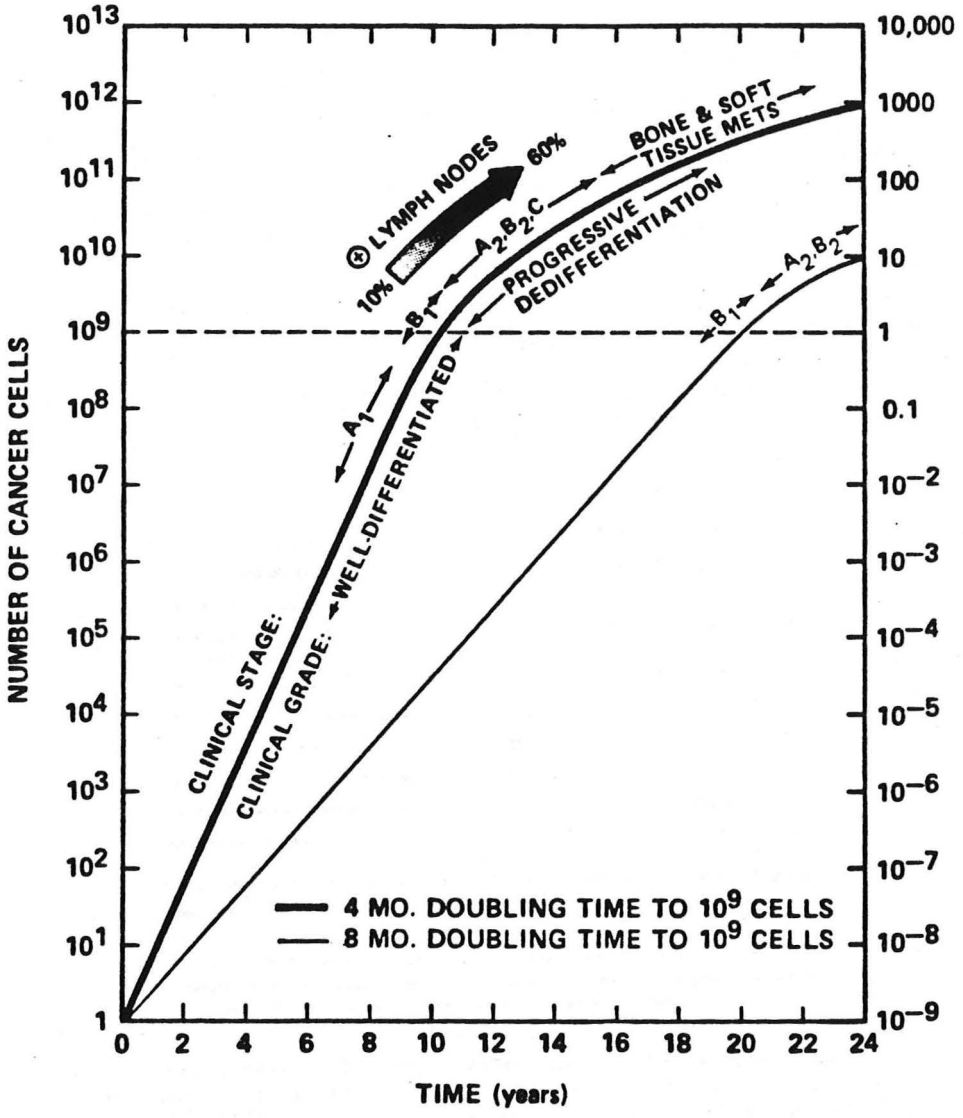


Cancer and total mortality rates by combined grading and stage.

It can be noted that there were no cancer deaths in Gleason's grade 3, 4 and 5, and that the cancer death rates were incredibly low in Gleason grades 6 and 7.

As Stamey (3) has emphasized, one can use this information to project the risk potential for any given patient. For instance, it is projected that 0.05 deaths per patient year is the life expectancy for the normal man aged 70. Thus, one can conclude that a man of 70 with a carcinoma of the prostate rated as Gleason stage 10 (or less) should have as much of a likelihood of dying from a noncancerous cause as he has of dying of his carcinoma of the prostate. Such determinations have become more important now that better primary therapeutic modalities are available.

The complete Gleason system provides an opportunity for a reevaluation of the projected thesis of Dr. McNeal (25, 26). Stamey (3) has emphasized that utilizing the strength of the addition of the stage to the Gleason categorization provides a concept of the volume estimate of the amount of tumor. Using this data, he has regraphed some of the potential patterns with an arbitrary 4-month and 8-month doubling time, thereby helping to clarify the long natural history of prostate cancer but emphasizing the continuum of its biologic expression; that is, a pattern directly proportional to volume and histologic grade of the primary tumor.



Doubling time of the prostatic cancer cell is assumed to be linear for the first 30 cell divisions until a volume of 10^9 cancer cells (1 g or 1 cc) is reached. Thereafter, tumor growth decreases exponentially as tissue factors modify the growth rate (Gompertzian kinetics). The four-month doubling time requires ten years to reach a volume of 1 cc (1 g), whereas the eight-month doubling time needs 20 years to reach the same volume. Although the horizontal axis is in years, observe that whereas 30 cell divisions are required to reach a tumor that weighs 1 g (10^9 cells), only ten additional cell divisions (a total of 40) are needed to produce a 1,000 g tumor (10^{12} cells). Note also that lymph nodes may be positive for several years before metastases become apparent.

Clinical Approach to the Patient With Carcinoma of the Prostate

The internist is usually introduced to carcinoma of the prostate either by virtue of his findings on rectal examination or following histologic identification after a transurethral resection of the prostate. Except for clinical stage A disease, rectal examination continues to be very important in our recognition and characterization of carcinoma of the prostate. A variety of laboratory tests and procedures are available to assist in the staging of prostate cancer. It is of interest that, in spite of the low incidence of prostate cancer in Japan, mobile units for mass screening have developed and a screening sequence has been examined (33).

One characterization of ten separate screening tests in 300 elderly men with a high prevalence of prostate cancer provides a relative value scale for these studies:

Results of Screening Tests for Prostate Cancer

Test	Number of Patients	Sensitivity	Specificity	Efficiency
1. Digital rectal examination	300	0.69	0.89	85
2. Acid phosphatase—enzyme	300	0.56	0.94	84
3. Urine cytology—aspiration	200	0.55	0.91	83
4. Prostatic-secretion cytology after massage	211	0.29	0.98	81
5. Urine cytology after massage	209	0.22	0.98	80
6. Urine cytology before massage	202	0.17	0.98	79
7. Acid phosphatase—CIEP	100	0.20	0.95	78
8. Lactic dehydrogenase V/I ratio	132	0.47	0.82	73
9. Leukocyte-adherence inhibition	113	0.50	0.79	72
10. Acid phosphatase—RIA	100	0.20	0.85	70

Statistical Analysis

Sensitivity (a) Percentage of positive tests in patients who had prostate cancer.
Specificity (b) Percentage of negative tests in patients who did not have prostate cancer.
Prevalence (p) Percentage of patients who had prostate cancer in the population studied.
Efficiency (e) Percentage of patients who were correctly classified.

$$e = [pa + (1-p)b] \times 100$$

Unfortunately, neither the application of radioimmunoassay technology for assessment of prostatic acid phosphatase fractions (35) nor the tissue polypeptide antigen (TPA) assay has significantly expanded the diagnostic horizon. This does not mean that the measurement of the prostatic fraction of serum acid phosphatase does not continue to be helpful in the staging of disease and, more important, as a parameter for serial followup in those patients with extensive disease under therapy.

In an attempt to understand the therapeutic options in the various grades or stages of prostate cancer, four important modes have been employed to attempt to separate local involvement from regional involvement from metastatic disease. Only such a separation could be expected to permit interpretation of the newer therapeutic trials. The five studies which provide such potential data include the transrectal sonography, radioisotopic bone scans, bipedal lymphangiograms, percutaneous lymph node aspiration and needle biopsy, and staging lymphadenectomy.

1. Transrectal ultrasonography: In staging this appears to have its major value in characterization of the status of the seminal vesicles; its exact sensitivity and specificity have not yet been established.

2. Radioisotopic bone scan: Paulson's review (2) of 509 patients demonstrated that the bone scan identified osseous involvement in 25% of all of the patients found to have no bony involvement by routine roentgenograms. As expected, the incidence of bony disease increased as the volume of the local disease increased and in stage 4a patients whose only other evidence of metastatic disease was an elevated serum acid phosphatase 35% of the patients had an abnormal bone scan. These findings typify a variety in the literature (37).

3. Bipedal lymphangiograms: The lymphangiogram has commonly been expressed as having an accuracy of approximately 75%. Where careful node-by-node comparisons between the radiology and histology findings have been carried out, this number has been considerably lower. This is not surprising, since it is not a particularly good test for microscopic disease and may, in fact, miss some nodes, such as in the internal iliac and obturator areas. Node-by-node analysis at Stanford and in London show a true positive rate of approximately 50% and a false negative rate of 50%; the false positive rate was 15% (38). Admittedly, when the lymphangiogram was unequivocally positive, surgical dissection confirmed the presence of node metastasis approximately 90% of the time (2).

4. Percutaneous lymph node aspiration and biopsy: In an attempt to avoid surgical exploration, the percutaneous fluoroscopy-guided fine needle aspiration biopsy of pelvic nodes is now under study. Localization with either lymphangiogram or CT scan has provided material for adequate staging in nearly 90% of patients studied (39). The false negative rate appears to be approximately 7%. One asset of this analysis is the potential to apply the Gleason grading system from the material obtained, thereby separating tumors into low grade, Gleason's sum 2, 3 or 4, versus high grade, Gleason's sum 8, 9 or 10. The procedure is relatively innocuous and safe.

5. Pelvic lymphadenectomy: Pelvic lymphadenectomy should better be termed staging lymphadenectomy because its only purpose is to serve as a diagnostic aid, not as a therapeutic procedure (2, 38, 40-42). Although initially considered "curative", this is no longer a reasonable thesis. Since this procedure is associated with significant morbidity and some mortality (38-42), its use should be limited for only those patients where the subsequent procedure could clearly be curative. Paulson's proposal to limit this procedure to a small subset of patients

was based on the evidence that a patient with a positive lymphangiogram and a histologic Gleason grading sum of greater than 5 has nearly 100% likelihood of having positive nodes, thereby excluding such patients from diagnostic node staging. The critical pool for the potential procedure are those patients with a negative lymphangiogram and a Gleason scale of 5 or less, where there is less than 10% chance of having node positive disease. This indeterminate group with the potential for cure by radical procedures (surgical or radiation therapy) become the primary pool for the procedure. Computed tomography and magnetic resonance imaging have not added a significant dimension to the characterization of extent of disease. Both of these provide pool resolution of pelvic nodes (generally requiring a lesion of greater than 2 cm in size) and at present appear to have their greatest value in needle-guided aspiration biopsy studies.

Since virtually all of the data upon which decision analysis for therapy has been made have used the American Urologic Clinical Staging nomenclature, we will review aspects of the clinical approach by this staging nomenclature.

A. Approach to Clinical Stage A Disease

Stage A carcinoma, as defined, represents disease identified only on the basis of tissue obtained during surgical procedure, generally transurethral resection. Presumably it is the most common clinical expression of prostate cancer and is characterized by a normal rectal examination, absence of evidence of disease beyond the capsule, and its discovery as an "incidental finding" at surgery. As Whitmore (6) has demonstrated, the prevalence of stage A prostatic cancer exceeds the clinical incidence or morbidity as well as the mortality from prostate cancer. Since this represents localized disease and, presumably, the earliest stage, any consideration for cure must focus on this population set. To appropriately assess the degree of intervention one must develop predictive data concerning not only the capacity of this lesion to grow but also our ability to eradicate it by some local technique.

Stage A_1: Since all stage A disease of low histologic grade has been shown to have 15-year survival statistics that are similar to those of the general age-related population (6, 43, 44), there appears to be no solid rationale for a radical attempt at eradication unless this lesion occurs at an age early enough to have the potential to reflect a change in the survival of the patient. Indeed, Whitmore (6) developed the thesis of the A_1 stage to identify this group of patients: It is the generally accepted clinical view that patients with A_1 disease not be subjected to any therapeutic intervention.

Stage A_2: The best approach to A_2 disease has not yet been established. It is clear (43-45) that stage A_2 disease affects the survival, particularly when the Gleason grade is high. Indeed, many studies of this subset have demonstrated that A_2 disease is more malignant than B_1 disease (3,44-46); in general terms, the 10-year survival for multifocal A_2 disease is approximately 60%. In looking at the survival curves it appears that localized prostate cancer begins to exert a negative biological effect on survival at approximately 5 years, and this effect is then progressive at that time. The decision in terms of management of A_2 disease, then, depends upon the age of the patient at recognition and the presumed actuarial survival of the American male. Olsson (45) has made a cogent argument to express the evidence that actuarial survival in the American male today is well over 77 years and, therefore, localized prostate cancer can be considered a significant biologic illness in men under the age of 72.

THERAPEUTIC OPTIONS

1. Radical Surgery.

Radical surgical procedures for the cure of prostate cancer are based on the classic thesis that if all of the neoplastic cells exist within the gland excision of the gland should result in cure. Radical perineal prostatectomy was popularized by studies of H. H. Young at Johns Hopkins and published in 1905 (47). In the clearest review of the role of radical surgery for stage A_2 disease, Walsh and Jewett (48) have made a strong case against such a procedure. As they well point out, the incidence of positive pelvic lymph nodes in these patients is higher than in stage B disease, probably at least 25%. For those patients with grade 3 disease or greater, they were able to generate their own evidence that no patient survived 15 years free of disease. In addition, they demonstrated that a radical prostatectomy secondary to a transurethral resection is not a "classical" surgical resection and, as such, carries with it increased morbidity (approximately 15% incidence of incontinence, 42% incidence of stress incontinence, 100% incidence of impotency), mortality and a failure rate (48). Since no one has yet reported long term, tumor-free survival in patients with stage A_2 disease, a radical surgical approach should be considered part of a research study rather than a mode of therapy.

Relevant to such a research approach, the most dramatic surgical advance in prostate cancer was recently reported by Patrick Walsh and his colleagues (49, 50); this procedure provides radical surgical removal with the best preservation of sexual function. This operation has attracted urologists and has become a popular approach. Since it does not extend the degree of removal of tissue, there is little reason to believe that the survival results to date will be altered by its advent.

2. Radiation Therapy.

Both external beam megavoltage radiation and interstitial implantation (brachytherapy) have been extensively utilized in the management of local and regional prostate cancer.

Clearly, the most definitive experience with external beam radiation has been generated by Malcolm Bagshaw at Stanford (51, 52). As early as 1956 Bagshaw utilized the linear accelerator for the treatment of prostate cancer. Over 775 patients have now been treated with a definitive program of radiation therapy and followed for up to 22 years. The rationale to radiation was obvious in that it could encompass an adequate port to include the entire prostate and prostate bed, the capsule, seminal vesicles and with the potential for those lymph nodes in immediate proximity to the gland. His initial results suggested an important role for such radiation therapy in patients with local and regional disease. Only two prospectively randomized clinical trials, however, compared radiotherapy with surgery for pathologically staged patients with carcinoma of the prostate. Paulson (2) directed the V.A. Cooperative Study that involved 56 patients treated with external beam radiation and 41 patients treated with radical prostatectomy. Analysis of the time-to-failure curves in two treatment groups indicated that radical surgery had an advantage over radiation therapy in controlling disease. Bagshaw himself carried out the only other trial, and his curves of time-to-treatment-failure of radiation therapy are virtually superimposable upon those for radical surgery in the V.A. series.

Several important observations have come from these and similar trials in other centers. As expected, there is a significant difference in survival in those patients with extracapsular extension. In patients comparatively staged with data following surgical lymphadenectomy, the survival at 8 years was nearly 80% for those with normal lymph nodes and 20% for those with lymph node involvement (51). The Stanford experience in 51 patients with limited disease demonstrated that the disease-specific survival quite closely patterned the overall actuarial survival. A 5-year followup in 51 patients staged as A_2 or B at Stanford (52) demonstrated that less than 20% of the patients were treatment failures. Disease-specific survival in this group was virtually that of the overall actuarial survival. Less than 20% of the patients followed for 12 years had evidence of treatment failure.

Critical to the expanded use and role for external beam radiation is the actual efficacy in sterilizing tumor of significant volume. Although Bagshaw has utilized a treatment program of at least 7,000 rads (delivered in 7 weeks) to the prostate and 5,000 rads (delivered in 7 weeks) to pathologically proven involved lymph node bearing sites, the ability to sterilize these tumors is limited. In an important study of 146 patients with clinically localized carcinoma of the prostate surgically staged and then treated with external beam radiation to the prostate and lymph node bearing areas, serial post radiation biopsies documented residual disease in 61% of the biopsies (53). In this study, 72% of the patients with a biopsy demonstrating tumor subsequently developed metastatic disease,

whereby only 24% of the patients with a negative biopsy subsequently developed clinical evidence of disease. Thus, the ability to sterilize with external beam radiation appears limited, particularly in tumors of significant size. In addition, a positive post radiation biopsy indicates active disease and identifies patients at significant risk for the development of metastatic involvement. Finally, it should be noted that radiation therapy is itself not without its problems. Urethral stricture, proctitis and peripheral edema are seen in approximately 5% of the patients, and if previously surgically staged, that incidence increases approximately five fold (54, 55). It remains to be seen whether hyperthermia, currently being examined, increases the efficacy of external beam radiation (56).

Iodine-125 implants, usually with an associated pelvic lymphadenectomy, have been extensively utilized by the Memorial group (57). Although Stamey (3) interprets the experience with this approach as slightly preferable to external beam therapy, it should be noted that the procedure has only been done since approximately 1970 and only 5-year survival data has been developed; this data involves only patients with stage B and stage C disease. When those stages are compared at the 5-year point to the external beam radiation, there does not seem to be a significant difference or advantage to either approach. Similarly, the use of combined interstitial (radio gold grains) and external beam megavoltage also appears to have promise as a therapeutic modality, but its duration of use is limited and it is not presently possible to identify a meaningful difference for this procedure over either of the two separately (58).

From the data presently available, radiation therapy appears indicated for patients with stage A_2 disease, particularly when the Gleason grade is greater than 5. The exact selection of the mode of radiation delivery cannot be better specified at the present time.

B. Approach to Clinical Stage B Disease

Stage B is theoretically the "internist's" lesion. It is palpable carcinoma confined to the prostate gland, identified on digital rectal examination. At the present time it represents between 10 and 15% of all prostate carcinomas at the time of presentation. A common parallel has been drawn between this stage of prostate cancer and another common hormone dependent neoplasm, breast cancer. Early diagnosis of breast cancer has been clearly associated with an improved survival. The problem of developing this parallel between the two tumors largely is the result of poor staging characterization. Even the B_1 tumor, interpreted as a palpable nodule of less than 2 cm at Sloan-Kettering or a tumor occupying less than one lobe of the prostate at Hopkins, suffers from differing interpretation from institution to institution. Walsh and Jewett (48) reviewed the 15-year survival data at

Hopkins in carefully staged B_1 disease patients. At 15 years 51% were alive and well, 32% had died but without disease, and 17% had recurrent cancer. No other modality of therapy has yet equalled these numbers, and now that the surgical procedure has reduced morbidity (probably less than a 20% incidence of impotence) it provides the best parallel data to the potential for cure seen in breast cancer. The problem with B stage disease more extensive than B_1 is the recognition that as many as 50% of these patients when carefully staged are actually at stage C. In spite of the fact that Walsh has expressed serious doubt concerning surgery in the management of B_2 lesions (48), studies from his own group reviewing their experience are of interest (60). In their experience 66% of the patients clinically staged as B_2 had extraprostatic extension, that is they were pathologic at stage C. Those patients had a 13% 15-year disease-free survival. However, in the B_2 patients who did not have extraprostatic spread (34% of the group) the 15-year disease-free survival rate was 50%. Gibbons (70) demonstrated relatively similar data.

As noted above, radiation therapy does not achieve quite the level of these reported results. Although the limited comparative trials of radical perineal surgery versus radiation speak in favor of surgery, it should be emphasized that the final answer is not yet established. Nevertheless, from the information available it appears reasonable that in patients under the age of 62 radical perineal prostatectomy has a survival advantage over that of radiation therapy and represents the treatment of choice at the present time.

C. Approach to Clinical Stage C Disease

Stage C disease represents the neoplasm that has extended through the prostate capsule but has not metastasized. Unfortunately, this represents nearly 40% of all prostate cancers at the time of diagnosis. When pathologic examination of the lymph nodes is integrated into the clinical staging considerations, most series have shown that greater than 50% of the patients have metastatic disease in the regional lymph nodes. Thus, any interpretation of data based on "digitally" staged patients actually examines a spectrum of disease that includes some stage C and, probably primarily, stage D disease.

Since radiation therapy has the potential for control of local-regional disease, it is of note that 60% of the stage C patients at Stanford had evidence of nodal involvement (52). This group with radiation therapy had a 50% 5-year survival and a 20% 10-year survival. For the present, radiation therapy appears to have the best potential for control of disease (3, 6, 45, 48, 51, 52). It is quite clear that the important attack on those patients at the more extended portion of the natural history of carcinoma of the prostate, that is stage C disease and stage D disease, require the most serious attention to alternative modes of therapy. For this reason, we will consider these potential approaches in conjunction with stage D disease.

D. Approach to Clinical Stage D Disease

By definition, stage D disease represents metastatic involvement. Stratification into D_1, which identifies regional pelvic lymph node metastases from D_2 where metastases to distant sites exist, defines a group of patient in whom regional therapeutic endeavors might still have the potential for control. A generic marker of both of these stages is the serum acid phosphatase which is elevated in approximately 70% of all patients at stage D. Unfortunately, as high as 20% of patients with stage A and B disease have been described with elevations, and as many as 40% in stage C disease (3). Virtually all of such elevations, however, have been reported in series where careful surgical staging has not separated groups of patients very well.

There is limited data concerning the duration of survival in stage D disease. The best recent survey, by Nesbit and Baum (62), examined 231 patients with stage D disease who received no systemic therapy. The 1-year survival was 47%, the 3-year survival 11%, and the 5-year survival 6%. These data can serve as a reasonable parameter for the interpretation of therapeutic results. Nevertheless, it must repeatedly be emphasized that the most serious problem in the decision analysis of therapy for prostate cancer is the limited comparative trials of stage, grade, age, matched, randomized therapeutic programs.

3. Treatment Response Criteria for Prostate Cancer.

Because of the difficulties in assessing the response characteristics in patients with advanced prostate cancer, criteria of response have been established in the United States and in Europe. These working criteria in the United States of the National Prostate Cancer Project Group were recently updated and are shown below (63).

Criteria of Response: National Prostatic Cancer Project Criteria for Determination of Response to Treatment [Slack, 1983, 94]

Complete objective response

All of the following criteria:

1. Tumour masses, if present, totally disappeared and no new lesions appeared.
2. Elevated acid phosphatase, if present, returned to normal.
3. Osteolytic lesions, if present, recalcified.
4. Osteoblastic lesions, if present, disappeared, with a negative bone scan.
5. If hepatomegaly is a significant indicator there must be a complete return in liver size to normal—i,e, no distension below both costal margins at the xiphoid process during quiet respiration without liver movement, and normalization of all pretreatment abnormalities of liver function, including bilirubin mg% and SGOT.
6. No significant cancer-related deterioration in weight (> 10%), symptoms, or performance status.
7. All complete regressions will be reviewed by a committee of three investigators: the protocol chairman and two investigators appointed by the central office. If the patient is from the protocol chairman's institution, a substitute reviewer will be appointed.

Partial objective response

Any of the following criteria:

1. Recalcification of one or more of any osteolytic lesions.
2. A reduction by 50% in the number of increased uptake areas on the bone scan.
3. Decrease of 50% or more in cross-sectional area of any measurable lesions.
4. If hepatomegaly is a significant indicator, there must be at least a 30% reduction in liver size indicated by a change in the measurements, and at least a 30% improvement of all pretreated abnormalities of liver function, including bilirubin mg/dl and SGOT.

All of the following:

5. No new sites of disease.
6. Acid phosphatase returned to normal.
7. No deterioration in weight (> 10%), symptoms, or performance status.

Stable state or no change

All of the following criteria:

1. No new lesions occurred and no measurable lesions increased more than 25% in cross-sectional area.
2. Elevated acid phosphatase, if present, decreased, though need not have returned to normal.
3. Osteolytic lesions, if present, did not appear to worsen.
4. Osteoblastic lesions, if present, remained stable on the bone scan.
5. Hepatomegaly, if present, did not appear to worsen by more than a 30% increase in the measurements, and symptoms of hepatic abnormalities did not worsen including bilirubin mg% and SGOT.
6. No significant cancer—related deterioration in weight (> 10%), symptoms, or performance status.

Objective progression

Any of the following criteria:

1. Significant cancer-related deterioration in weight (> 10%), symptoms, or performance status.
2. Appearance of new areas of malignant disease by bone scan or X-ray or in soft tissue by other appropriate techniques.
3. Increase in any previously measurable lesion by greater than 25% in cross-sectional area.
4. Development of recurring anaemia, secondary to prostatic cancer (not chemotherapy).
5. Development of ureteral obstruction.

Note: An increase in acid or alkaline phosphatase alone is not to be considered an indication of progression. These should be used in conjunction with other criteria.

The criteria of response in the studies from the British Prostate Group (64) and from the European Organization on Research and Treatment of Cancer-Urologic Group (65) are slightly different. In addition, the difficulties in characterizing a response have led to considerable focus on differentiating stable versus partial responses in advance of prostate cancer (66).

4. Hormonal Therapy of Prostate Cancer

Huggins' (67) legendary observations in the 1940's of the critical regulatory role of testicular androgens in prostate cancer provided the critical background to the hormonal approach of this neoplasm. Since the growth and function of the normal prostate gland are regulated by androgens, a reasonable rationale is to attempt total suppression of androgenic stimuli of the prostate. Enormous strides have been made in our understanding of the biology and biochemistry of androgens, and much of this knowledge is generated by Dr. Wilson in this institution with such observations as the demonstration that the major metabolite of testosterone was dihydrotestosterone (68). Scott et al (69) has recently critically reviewed the issues of hormonal therapy of prostate cancer and reemphasized the critical role of the testicular contribution of androgens. Thus, although the major circulating androgens have their origin in the testis and the adrenal, the testis accounts for over 95% of circulating plasma testosterone. In general, the testis of the adult male produces approximately 6500 µg of testosterone per day and approximately 100 µg of dihydrotestosterone per day. The androgens secreted by the adrenal are androstenedione (approximately 3 mg per day) and dehydroepiandrosterone (approximately 24 mg per day). Since Scott et al (69) believe that the androgens of adrenal origin are of doubtful significance in stimulating prostatic growth, as perhaps emphasized by the fact that the prostate gland remains atrophic in the castrated adult male, they feel that the removal of 95% of the circulating plasma testosterone as a result of bilateral orchiectomy is "biologically" effective androgen suppression. Although this is the generally prevalent view and the basis of the rationale for most of the classic hormonal manipulative techniques, current concern has been expressed for a rationale for blockade of the adrenal as well as testicular androgens. Geller (70) has demonstrated that adrenal androgens may actually diffuse into prostate cells in significant amounts. Thus, although adrenal androgen's conversion rate to dihydrotestosterone may only be in the range of 3-7%, his studies suggest that they may account for up to one-sixth the total concentration of prostatic dihydrotestosterone, thereby providing a biochemical rationale for suppression of the adrenal contribution.

A. Biochemical Issues and Mechanisms:

Without intent to review the biology and biochemistry of androgens, the concise statement of Scott et al (69) provides a basis for some clinically relevant observations. In essence, "testosterone converted to dihydrotestosterone by the membrane-bound enzyme, 5α-reductase (NADPH-dependent Δ^4-3 ketosteroid 5-α-oxidoreductase). Dihydrotestosterone is then bound to a specific cytoplasmic macromolecular

protein, the receptor. The receptor-steroid complex is transported to the nucleus and there the complex is bound to acceptor sites on chromatin. By some as yet unidentified mechanism, these events activate transcription and result in the formation of messenger RNA and increased protein synthesis".

Surprisingly little is known of the androgen receptor binding activity in human prostate cancer or its relationship to estrogen therapy. A recent examination of tissue obtained from 223 untreated patients with proven prostate cancer at the Mayo Clinic provided some interesting new observations (71). The mean receptor binding activity in both the cytosol and the nucleus was significantly higher for patients with cancer than for other prostate diseases. In addition, the mean values for each receptor site increased relative to the stage of disease. For instance, the cytosol androgen binding (expressed in fentomoles per milligram protein) for benign prostatic hypertrophy is approximately 8.3. By contrast, stage A carcinoma of the prostate cytosol binding was 8.5, for stage B 9.8, for stage C 15, and for stage D 17.5 fentomoles per milligram protein. Nuclear binding in benign prostatic hypertrophy is approximately 19.3 fentomoles per milligram protein. Comparative numbers for carcinoma of the prostate for nuclear binding demonstrated 19.0 for stage A, 31.8 for stage B, 38 for stage C and 44.5 for stage D. Another interesting finding in these studies was that androgen binding in malignant nodes differed from that in the primary tissue and actually varied from node to node in the same patient. The true biologic significance of these findings is not clear, but serial studies are planned during the sequential followup of these patients. The role of the increased androgen receptor activity is by no means clear, but some suggestion exists that in some circumstances estrogen therapy itself may increase such activity (72). A serious problem in characterizing any of the aspects of the receptor levels and their biologic significance in prostate cancer is the classic observation of heterogeneity of most prostate cancer specimens. Unfortunately, a good histochemical method does not exist for a careful assessment of this heterogeneity. Nevertheless, since a major cause of hormonal therapeutic failure appears to be the emergence of such cells from a heterogeneous population, their recognition and characterization are critical (73).

The exact mechanism whereby androgens affect prostatic cell death is unknown. Isaacs' extensive studies (74) examined the agonistic ability of androgen to stimulate prostate cell proliferation and the antagonistic ability to inhibit prostate cell death. Approximately 2.1% of the total prostatic cells die per day when serum testosterone levels are sufficient for maintenance of the gland. Three days following castration, when the serum testosterone level is less than 10% of the normal value, the percentage of total prostatatic cells now dying per day is actually increased ten fold to approximately 21%. This high rate of prostatic cell death can be inhibited following castration if serum androgen levels are maintained by exogenous treatment. Thus, these observations (74) suggest that the rapid involution of the prostate following castration is predominantly due to a decreased antagonistic effect of androgen on prostatic cell death, rather than to a decreased agonistic effect of androgen on prostatic cell proliferation. Presumably, these two androgenic effects, then, are distinct processes in the prostate gland.

Attempts to predict a hormonal response have been largely fruitless. One series of studies from the British Prostate Study Group (75) suggest that those patients who have poor testicular function as evidenced by low concentrations of testosterone in their plasma at the time of diagnosis or high pre-treatment concentrations of luteinizing hormone had poor response to hormonal therapy and an associated very poor prognosis.

B. Primary Hormonal Approaches:

A variety of approaches have been utilized in an attempt to affect the hormonal milieu. From a clinical point of view it is quite clear that an estimation of the plasma testosterone provides the most reliable objective measure of estrogen therapy in prostate cancer (76). Effective therapy is defined as a level that reduces the plasma testosterone concentration to that of "female" levels.

1. Bilateral Orchiectomy:

Bilateral orchiectomy clearly achieves the suppression of plasma testosterone required. It does so with direct promptness, not requiring continued therapy; avoids the complications associated with many of the other drug therapy programs; and finally, avoids the issue of breast enlargement and tenderness commonly seen in patients treated with estrogens.

2. Estrogen Therapy:

The effectiveness of estrogen therapy in producing a clinical remission in prostate cancer is well proven. Indeed, such hormonal trials represent the only significant randomized trials in prostate cancer of any magnitude. One can summarize several points from these studies (2, 3, 27, 69, 75-80). It is quite clear that estrogens can produce significant and dramatic clinical response and measurable regression of metastatic disease. Evidence that hormonal therapy prolongs the overall survival of patients, particularly patients with stage C or stage D prostate cancer, does not exist. Endocrine therapy in stage C disease appears to delay the progression to stage D, although the overall survival is not changed by such therapy. The addition of estrogen to orchiectomy offers neither survival advantage nor improved control of disease. Problems exist as to the exact dosage of diethylstilbestrol that is appropriate to therapy. It is evident from the controlled V.A. studies that a 5 mg daily dose of diethylstilbestrol will suppress plasma testosterone levels to those of an anorchid level. However, cardiovascular morbidity and mortality, particularly in the first year, provide a survival disadvantage when compared to orchiectomy. At doses of 1 mg diethylstilbestrol per day a survival advantage does accrue, but consistent suppression of plasma testosterone does not exist (76). Because of the diurnal secretory patterns and the failure at low dose suppression, only a dose of 1 mg three times per day can be expected to provide the same degree of suppression as bilateral orchiectomy. Unfortunately, the true cardiovascular risk at 3 mg per day has never been assessed.

3. Gonadotropin-Releasing Hormone Analogue-leuprolide:

An alternative approach to hormonal manipulation has been generated by the availability of potent analogues of gonadotropin-releasing hormone. Agonistic analogue peptides have been found with paradoxic effects on the pituitary with resultant initial stimulation and then subsequent inhibition of the release of follicle stimulating hormone and luteinizing hormone (81-83). The result of this is a decrease in testicular androgen production. One analogue, leuprolide, has already undergone extensive trials and has demonstrated efficacy quite similar to that of diethylstilbestrol. These studies (81) demonstrated that the suppression of testosterone and dihydrotestosterone and the decrease in acid phosphatase were comparable in the leuprolide group to those seen with diethylstilbestrol. Both the objective response rates and the overall survival rates were essentially the same. Somewhat less gastrointestinal side effects were noted with leuprolide.

4. Antiandrogens-Flutamide; Anandron:

Antiandrogens provide an entirely different mode of action and have generated considerable recent interest. They produce their effect by direct competition with androgen at the target organ and inhibit the nuclear uptake of dihydrotestosterone. The earliest, albeit a relatively ineffective antiandrogen, was Syproteroneacetate. The recent availability of Flutamide, a nonprogestational, nonsteroidal, pure antiandrogen that neither inhibits gonadotropin release nor suppresses plasma testosterone synthesis, has had the most extensive clinical trials to date. In initial studies (83, 84), approximately 87% of the patients had a favorable response and the toxic side effects were modest. Approximately 40% did develop gynecomastia not unlike that seen with estrogen therapy. Of interest is that in those individuals who were sexually potent prior to Flutamide therapy almost all remained potent during the period of treatment. In addition, two patients who were impotent prior to starting Flutamide reported satisfactory potency during their therapy. No other significant deleterious effects were seen with the antiestrogen therapy.

5. Combined Therapy:

Labrie and coworkers (85) have combined the use of an antiandrogen (Anandron) and a luteinizing-hormone releasing analogue attempting to affect hormonal function at multiple sites. Their preliminary studies suggest that 100% of their patients have had a response! To date, no significant comparative evaluations have been carried out, but a current NCI trial is in the planning phases for a direct comparative trial between these agents, individually and combined (86).

6. Other Therapeutic Approaches:

A variety of other therapeutic approaches have been examined. For instance, both medical and surgical adrenalectomies and surgical hypophysectomies have been utilized in the past. Although it is generally considered that no good biochemical basis exists for such an

ablation approach, clinically symptomatic or subjective responses have been variously described in approximately 40% of the patients. It is noteworthy that Geller (70) has attempted to generate a current rationale for blockade of the adrenal, as mentioned before. Current trials in this regard are examining the use of estrogen and megestrol acetate, a progestational antiandrogen which is known to block androgen production and androgen-mediated action. Megestrol acetate reduces the plasma gonadotropins, does not affect plasma prolactin, and significantly decreases plasma testosterone. The rationale for this therapy is the attempt to reduce all androgen production, both testicular and adrenal. A parallel study employed the use of aminoglutethimide for medical adrenalectomy under similar circumstances (87). Of 43 patients so treated (87), one patient had a complete response with a remission duration of approximately 9 months. The responses in the rest were trivial.

C. The Timing of Hormonal Intervention:

No data exists concerning the best time at which hormonal intervention should be generated. In general, the urologic community elects early hormonal manipulation with a consideration that when the tumor is at its smallest size the greatest effect of hormone suppression should be evident. In general, the Medical Oncology community has leaned toward the use of therapy at the time of clinically symptomatic disease. Since hormonal manipulation can be expected to yield clinically impressive improvement in nearly 80% of the patients with carcinoma of the prostate, the rationale behind waiting is the clear recognition of an objective response in a disease where the early use of hormones has not affected overall survival. It is clear that no objective data provides an answer to the timing of therapeutic intervention. Clearly, the decision is in the hands of the clinician and this decision is usually made on the basis of personal philosophy rather than substantive data.

D. Hormonal Failures:

Significant attention has been focused on the basis for the escape phenomenon from satisfactory hormonal control. It is quite clear that at least in the patients with orchiectomy an increase in plasma testosterone is not identified at the time of failure, although recently Geller et al (88) did identify a subset of patients where hormonal suppression had not been adequate. It is in this group in particular that careful drug compliance must be urged and the consideration for suppression of adrenal sources of androgen are proposed (88). In general, however, adding more hormone suppression to an already suppressed state has not proven to provide a second response. Thus, the addition of estrogen to the patient who has an orchiectomy has not added any clinical responsiveness and, similarly, orchiectomy superimposed on an adequately estrogen-suppressed androgen production state has not resulted in response. The one exception to this is the relatively rare response of transient nature described with the use of high dose diethylstilbestrol diphosphate in patients who have relapsed. This therapy, largely pioneered by Dr. Harry Spence in Dallas (89), has recently been confirmed for selected circumstances of clinical crisis (90).

The commonly accepted concept that the failure of hormonal control is due to a change in the systemic effectiveness of the hormone, a thesis that has led to the superimposition of successive hormonal manipulations, does not have substantive support in any investigative model. The best animal studies have now demonstrated quite clearly that the classic picture of cellular heterogeneity recognized at virtually every stage of prostate cancer is in fact the basis for the treatment failures (91). The parallel model documented by Isaacs' studies (91) using the serially transplantable androgen sensitive Dunning R-3327H rat prostate adenocarcinoma has demonstrated quite clearly that the escape phenomenon is not due to a change in systemic effectiveness of the therapy, nor is it due to an adaptation of initially androgen dependent cells to a new androgen independent phenotype induced by some sort of a changing environment. Rather, it is quite clear that the relapse is due to the basic heterogeneity of the original tumor, that is the emergence of preexisting clones of androgen independent tumor cells. These observations stress the critical limitation of hormonal manipulation and forcibly demand a broadened therapeutic program.

5. Chemotherapy

One of the most important stimuli to the development of Medical Oncology was the early experience in the management of breast cancer. The evidence of hormonal responsiveness encouraged trials of cytoreductive chemotherapy as these patients escaped from endocrine control. The translation of this experience to prostate cancer has resulted in little enthusiasm that cytoreductive chemotherapy can result in dramatic objective responses or a change in the clinical status of patients with metastatic carcinoma of the prostate.

A variety of studies have reviewed the cytoreductive chemotherapeutic experience, both with single agents and combinations of drugs, in the approach to patients with adenocarcinoma of the prostate (64, 80, 92-99). A very fair summary statement of our experience to date was expressed by Michael Friedman and his coworkers (99) with the statement that the palliative role of non-hormonal cytotoxic chemotherapy in the treatment of endocrine resistant prostate carcinoma has not been established. Several problems exist concerning the trials to date. The most critical problem has been the definition of a "response" to the treatment. Unfortunately, most patients studied have had few marker lesions allowing a characterization of the disease, thereby delimiting the quantification of a response. It has been estimated that the number of patients in whom a clear documented response, either complete or partial or both, has been identified in these series is only approximately 5% (99). It should be emphasized that in these various studies single agent and combination drugs frequently are ascribed to produce responses in the range of 10-25%. In most, these responses are actually finely defined as a "stable disease category". The problem with stable disease as an indicator of a response is that little data can be generated to demonstrate that the stability is actually the result of the treatment program. In addition, although one would desire survival as a primary

criterion in the analysis of clinical trials, this is rarely used as an end point in these studies except when expressed in terms of a comparison between "responders and nonresponders". Unfortunately, the analysis of survival data by such an expression is incorrect. When one compares the results between responders and nonresponders the data is biased in favor of responders, and the results are misinterpreted in terms of the calculation of survival (100). Careful analysis of even the few prospective randomized clinical trials carried out during recent years fails to demonstrate a survival advantage when compared to any concurrently treated control group.

Current interest focuses on some reasons for the failures in prostatic carcinoma, particularly in light of the relative success with patients with breast cancer. First, it should be emphasized that some responses are seen by even the most rigid criteria; as mentioned in a recent analysis of all of the cooperative trials to date, approximately a 5% documented response rate can be recognized (99). One common explanation for the failure in patients with prostate cancer is that the population under treatment is quite elderly and, as such, tolerate cytoreductive chemotherapy poorly. Many have a variety of other clinical problems, such as heart disease or renal disease, that limit the utilization of agents with the best potential for therapeutic response. A second consideration in terms of our dismal results to date focuses on the appropriate time of chemotherapy administration. In general, these patients have been treated late in their course when a presumed hormone-independent cell population has emerged. Since the current evidence suggests that this potential hormone resistant clone exists within the milieu of heterogeneity that characterizes these tumors from the very start, several immediate questions are posed. For instance, is that resistant clone one with absolute lack of hormonal responsiveness or is it one with a relative lack. Were the latter to be correct, then some of the present strategies for the management of a similarly difficult circumstance in breast cancer might be applicable; that is, the use of hormonal stimulation in immediate juxtaposition to the delivery of multiple cytotoxic agents. Under those circumstances, that type of sequence could be used even late in the course of hormonal therapy, although not as late as we now approach patients with prostate cancer. Alternatively, if this clone is clearly resistant early on, one could make a strong case for early cytoreductive agent therapy prior to the institution of hormonal suppression. The aim under those circumstances would be to attempt to eradicate that initial resistant clone and then control those hormonally responsive clones with intensive endocrine manipulation. None of these questions have been examined. These can be approached both in the animal tumor model in the style already begun by Isaacs (74, 91), as well as in cooperative clinical trials where the question can be approached in a prospective and defined fashion.

At the present time we do not have data to convincingly utilize chemotherapeutic agents in the management of patients with carcinoma of the prostate. We must agree with the view expressed by Friedman and coworkers (99) that the routine use of cytotoxic, nonhormonal chemotherapy, as opposed to other less toxic and less costly palliative modalities has yet to be supported. We believe that patients with so-called stage D_2 disease not previously treated and with evidence of quantifiable lesions represent an ideal pool for cooperative clinical investigation.

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