Prostate Cancer: Progress and Change

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For several years it has been recognized that prostate cancer constitutes a significant oncologic problem. The relative constancy of both the numbers of new cases and the recorded numbers of deaths have been the subject of numerous reviews and reports.¹

However, we have recently experienced a period of substantial clinical change in the overall approach to prostate cancer: new methods of diagnosis; emphasis on primary care; assessment of histologic prognosis; clinical classifications for prognoses reflecting the extent of disease; and the availability of new therapeutic interventions. With change hopefully comes progress, and there is significant documentation of this progress (Fig. 1). Current national figures on prostate cancer reveal—in terms of population groups, for localized cancers—that there is improvement in the five-year survival rates (Fig. 1). These results, of course, must be followed closely for longer periods of time and can only be evaluated when the specific factors responsible are identified, and when further follow-up and observation times are affordable. This is not the case at the moment.

Epidemiology

There is no question that there are changing cancer death rates by age and race in the United States. Prostate cancer remains a serious problem among blacks.² Attempts to identify other high risk groups, possible sexual or transmissible factors and socioeconomic factors involved have been instituted and preliminary reports given.³ ⁴ These areas must be watched closely since there may be a particular group of individuals who, with further identification, could benefit from improved methods of screening and prevention of prostate cancer.

It should be noted that even this limited amount of information has not been previously available.¹ Careful case control studies of blacks in Washington, D.C. compared with those in Africa have suggested that external, environmental factors other than original racial origin may be affecting prostate cancer growth rates. This is a significant epidemiological advance.³

Morphology and Histological Prognosis

The morphology of prostate cancer has been described by individual experts and collaborative groups for some time. This area has been recently reviewed and there is excellent information available for students concerned with this perplexing problem.⁶

All available evidence suggests that, generally, prostate cancer exists as a multifocal carcinoma, as Mostofi and his asso-

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Some investigators believe that these multiple foci of prostate cancer represent intraglandular metastases, but this has not yet been resolved.7 No matter how early prostatic cancer is detected, it seems to exist at more than one cellular site. There have been a number of attempts to identify those factors in systems espoused by Gleason, Mostofi and others, that could provide a single system for histological prognostic use.7 Such a venture represents change and change is usually difficult to apply widely. In 1978, the American Cancer Society National Prostatic Cancer Task Force will undertake this difficult effort. The comparison of proven systems in the United States and elsewhere will be helpful. The assimilation of all factors that are found reproducible and that can be adapted by many pathologists will alter and significantly affect our current thinking about aggressive approaches and other alterations in early or late treatment of prostate cancer. Since this appears to be possible, it is a most important event.
### TABLE 1A
DIFFERENT CLASSIFICATIONS OF ADENOCARCINOMA OF THE PROSTATE

| Stage | Description |
|-------|-------------|
| A I, 0 | Occult Cancer |
| A₁ | Histologic: well differentiated, ≥ 3 slides |
| A₂ | Histologic: > 3 slides or not well differentiated |
| B II, A | Cancer confined within prostate capsule |
| B₁ | Tumor occupying ≥ 1.5 cm. in 1 lobe only |
| B₂, B | Tumor occupying > 1.5 cm. in one or both lobes, not invading capsule |
| C III | Cancer with extracapsular extension, no nodal or distant metastases |
| C₁ | < 70 gm. |
| C₂ | > 70 gm. |
| D | Cancer with demonstrable metastases |
| D₁ | Pelvic lymph node metastases or ureteral obstruction causing hydrenephrosis |
| D₂ | Bony or distant lymph node or organ metastases |

### Chemical Diagnosis

For some time, acid phosphatase determination has been essential to the diagnosis of prostate cancer. Unfortunately, its elevation, as determined indirectly by substrate assay has usually been clinically associated with extension or metastasis—that is, the prostate cancer is no longer confined to the gland. Within the past few years, several new assays have been developed by a number of investigators, and are currently under a nationwide field trial by the American Cancer Society Task Force on Prostate Cancer.

Radioimmunoassay
Radioimmunoassay (RIA) techniques

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for prostate cancer can provide immunologic specific prostatic acid phosphatase assays. It is hoped that improved RIA will identify the extent of disease in patients earlier and more accurately. Radioimmunoassay, now undergoing a national screening test, is an expensive test, and therefore other alternatives have been reported and are similarly under trial.

Counter-immunoelectrophoresis

Counter-immunoelectrophoresis (CIE) can provide an immunochemical method for the detection of prostatic acid phosphatase. Early tests demonstrate that it is relatively inexpensive and can be performed in any hospital laboratory equipped with commonly available equip-
ment. The counter-immunoelectrophoresis method may provide a more widely usable test, with equal specificity and accuracy. CIE is also currently under a nationwide American Cancer Society field test.

Further Chemical Assessment

One must not overlook further chemical assessment and determinations of prostatic fluid. In most patients, continuing evaluations of this substance are warranted upon urologic examination. Early tests suggest that certain isoenzymes may be altered. In fact, elevations in LDH in prostatic cancer patients seem to support the concept that the prostate cancer may not only be multi-focal in its histologic origin, but also may exert a general metabolic effect upon the gland. 10

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Bone marrow acid phosphatase determinations have been utilized as well as lymph node biopsy in the neck and other areas to detect metastatic disease where it is not thought to be clinically present. The goal and philosophy of therapy can be substantially changed by such tests. Newly purified acid phosphatase determinations previously referred to 10,9 have been used recently to assess the value of bone marrow acid phosphatase in staging prostatic cancer but the results are still tentative. These tests appear to be more accurate than those used previously and upon which clinical recommendations have been made. At present, it would appear that such determinations will confirm the unexpected presence of microscopic prostatic cancer; further tests and trials will determine how often this occurs. The preliminary results 11 from such new tests suggest that it does not occur frequently. One must again separate the newly available methods of staging for the extent of disease beyond the primary tumor from former methods. Past results using other techniques cannot be applied to present circumstances. Currently, bone marrow acid phosphatase measurement by these new techniques appears to only minimally improve the diagnosis of metastatic disease.

Staging Classifications

In the past, there have been differences in both the staging and end results reporting for a variety of tumors. The American Joint Committee for cancer staging and classification has used Roman numerals through IV to correspond with Whitmore's A through D. 6 The International Union Against Cancer (using the TNM classification) has a slightly different approach to clinical staging. These systems are currently under evaluation by several groups. The most current and comprehensive comparison of these classifications was derived from that prepared by Boxer 6 (Table 1). The most significant difference in all of these approaches seems to occur with the early focal or occult cancer. In the United States, further definition and further subclassification is occurring and, as a result, other recommendations are being made for therapy. The so-called focal localized nodule of the prostate frequently occurs in the B stage. However many believe that its frequency is less than had been thought. 4 Localized pelvic prostatic cancer, stages C or D, or Di, are now more frequently defined as a result of bilateral pelvic lymph node dissection. To date, no one can precisely define when a pelvic node dissection is diagnostic, when it is therapeutic, or even when it constitutes a procedure acceptable to all. There are extensive procedures performed in the course of some interventions; lymph node sampling is done in others. The numbers of sections of the lymph nodes considered necessary for the detection of microscopic cancer cells is a problem of institutional variation. Moreover, lymphangiograms have recently been substantially used for preoperative staging with some modification in technique. 14 The advent of CT scanning will doubtless provide further changes, additional refinement and more
assistance in the determination of the extent of disease without surgical intervention. Implicit in all of these factors is that the degree of differentiation of the primary prostate carcinoma may affect the survival regardless of the therapeutic intervention. This has been previously not-

ed and has been most carefully determined in a recent study by Whitmore and associates. Important determinants of metastases subsequent to a particular form of therapy probably do indeed seem to relate to:

- The large size of the primary tumor;
- Poor histological differentiation;
- Volume of lymph node metastases;
- Lack of local prostatic response to radiation;
- Possible seminal vesicle invasion. Such careful studies provide important new factors that will affect the further classification, staging and assessment of our end results.

Randomized selection of cases from institutions doing one form of treatment compared to others who have performed lymph node dissections have been reported. While these emphasize the importance of lymph node drainage and lymph node assessment in the staging of extent of disease, they also document that even today there are still unanswerable questions or at least instances of clinical variance. One must not forget Lord Batson's plexus and the prostatic venous drainage! It may prove to be of continued importance. The possibility that the interruption of lymph node drainage may have non-beneficial immunological effects has been raised but not resolved.

In addition to the factors mentioned for staging prostate cancer and the variety of prognoses reflected, improvement may come from other areas of biology. Tumor markers or hormonal (androgen and estrogen) receptor sites have been found to be useful for therapeutic treatment and also for clinical treatment trial stratification. Work on a variety of receptors is underway and promising results have been reported in terms of estrogen receptors in human prostate cancer. While final results will not be available in the near future, current data suggest that some hormonal markers may be useful in the future in clinical classification and further therapeutic stratification.

Physical examination has not been extensively mentioned in this particular report. It remains, however, an essential part of any program of complete evaluation and initial and continuing inspection. Biopsy techniques likewise have not been reviewed since they have been extensively reported upon. The use of roentgenograms and other forms of scanning are helpful and reports are also available. Prostatic echography is a new tool and initial promising results have been reviewed. The scanning of bone marrow in prostatic cancer may also be useful for a variety of staging purposes, but more importantly, for therapeutic decisions regarding the efficacy of adjuvant treatment, i.e., chemotherapy. Other immunologic markers and assessments of immunocompetence of status of the host, remain the subject of intensive and widespread individual research studies. They should be watched for further promising reports but at present cannot be translated into widespread therapeutic or diagnostic recommendations.

**Primary Treatment**

As in the past, perineal prostatectomy and radical retropubic prostatectomy are being performed today (Table 2). The perineal approach has not changed and is being used by some for more selected cases or patients with other medical life-threatening complications. As is reflected in recent reviews (Table 2), there are some patients who are now benefiting from ret-
ropubic prostatic removal combined with lymph node intervention. Recent reviews and summaries of the results of this approach appear to justify its use. However, longer follow-up is needed.

Interstitial therapy for localized prostate cancer has been introduced using I\textsuperscript{125}. Extensive results have been described by Whitmore and associates and are being followed closely.\textsuperscript{12} Thus, one has a variety of surgical approaches to early or localized stages of disease combined with variations in lymph node dissection, with or without the addition of interstitial operative applications.\textsuperscript{6} The techniques, the numbers and the degrees of lymph nodes are currently subjects of dispute and debate. There are at present no randomized studies, nor should there necessarily be any. However, it is important to note that these results are promising, and, in and of themselves, they afford a therapeutic option.

Bagshaw's observations with external radiation for localized disease indicate that short-term, disease-free survival is possible in over 87 percent of patients with negative lymph node biopsies. Patients in an intermediate phase, with positive lymph node biopsies only in the pelvic region following extended field radiation therapy also have an improved survival rate, nearly 72 percent. Patients with positive periarteric node and pelvic node biopsies have a diminished survival. The randomized trial conducted by Bagshaw and associates has been recently reported and continued promising results are seen.\textsuperscript{15} There are other features of radiation therapy reported and described that cannot be ignored. The question of the use of exogenous estrogens as a form of endocrine therapy, has been most recently reported; those interested in reviewing the divergent opinions may wish to consult a recent review.\textsuperscript{6} Hormones should be considered essentially palliative and should not be confused with primary treatment.

Surgery and radiation therapy as primary treatment afford a reasonable opportunity for disease-free interval and possible cure. The author does not prefer surgery, interstitial therapy or external radiation therapy on the basis of any results currently available. In the author's present viewpoint, no one mode is definitely proven to be superior to any other. Urologic surgeons and others should afford patients the opportunity for the selection of treatment best suited to their particular needs, depending upon a variety of interpersonal factors and possible medical conditions. In terms of primary therapy, it must be remembered that lymph node dissection is not without its possible complications. Moreover, lymphangiograms may or may not be desirable. Radiation therapy has an important role to play as does primary surgery. An attempted resume of the current status of the therapy as employed today by radiotherapists and urologists is reflected in Table 3. The biggest problem with the interpretation of Table 3 is that many of the stages depend upon precise surgical staging. They are not clinical stages. Whether or not node dissection or node sampling is done remains an important and irresolvable distinction.

**Palliation Therapy**

Palliation, or hormonal, therapy is neither intended nor claimed to be curative. Whether one uses a different dose of estrogen combined with the presence or absence of orchietomy, remains a source of occasional concern. It is appropriate to restate results from our own institution as an example of full term follow-up and high percentage autopsy examination of patients with widespread or metastatic prostatic cancer who are treated with either orchietomy or combination treatment (Table 3). Without question, prostate carcinoma remains the all-time and major cause of death in all such patients. There
are no significant statistical differences in this particular hormonal program. We are aware of the ability to measure dihydrotestosterone (DHT) and other substances in the serum, but these should not be used as a guide to the adequacy of palliation therapy. The patient himself will inform the clinician regarding pain relief, sense of well being, weight, appetite, etc. A variety of doses are useful and have been found adequate. Levels of hormones in one partition of the total body compartment cannot possibly be of predictive value, although some may feel that is the case. Only extended metabolic studies over 24 hours including all possible components

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**TABLE 2**

**CURRENT STATUS OF MOST COMMONLY EMPLOYED METHODS OF PRIMARY THERAPY**

| Stage | Examples of Therapeutic Choices Currently Being Employed |
|-------|--------------------------------------------------------|
| A₁    | Some prefer surgery, others observation.                |
| A₂    |                                                        |
| B₁    | 1) Radical prostatovesciculectomy (either retropubic or perineal approach*) ± lymph node dissection  
2) Radiation therapy |
| B₂    | 1) Radical retropubic prostatovesciculectomy with pelvic lymphadenectomy  
2) Radiation therapy ± node sampling |
| C     | 1) Radical retropubic prostatovesciculectomy with pelvic lymphadenectomy  
2) Interstitial radiation with pelvic lymphadenectomy  
3) Radiation therapy ± lymph node sampling  
4) Some prefer observation ± endocrine treatment |
| D₁    | See text                                               |

* A few centers employ cryosurgical destruction ± lymph node dissection in all the stages depicted in this table.
may lead to a valid endocrinologic conclusion. In our own experience, this does not justify a change in clinical judgment and is a research project only. The following viewpoints for conventional hormonal palliation with advanced, untreated prostatic carcinoma are restated:

- Withhold therapy until the patient's symptoms or general condition warrant treatment.
- Generally, use castration alone although many physicians also administer stilbestrol either with or without castration.
- When stilbestrol is administered following symptomatic or clinical relapse after castration, limit the dose to one mg. daily. There is some suggestion, however, that three mg./day may provide better androgen suppression in certain patients.
- High-dose estrogen therapy (natural or synthetic source) is not recommended except for selected use in short-term, acute situations.

Hypophysectomy and adrenalectomy have been discussed previously. The effectiveness of these two procedures has been established and need not be repeated at this time. Occasional long-term results from this form of extensive hormonal therapy have been described. However, following new forms of chemotherapy for patients relapsing after conventional hormonal therapy, it has been found that chemotherapy is generally superior. Non-steroidal anti-androgens and other agents that have suppressive effects upon the adrenals have undergone some clinical study. They do not, however, appear to afford a practical or useful alternative for palliation at this time. Metastatic prostatic cancer that has relapsed following conventional hormonal therapy can be

### TABLE 3

**CAUSE OF DEATH BY PRIMARY TREATMENT**

| Cause of Death               | Orchiectomy | Estrogen + Orchiectomy |
|-----------------------------|-------------|------------------------|
| Prostatic carcinoma         | 47.4%       | 64.7%                  |
| Other neoplasms             | 32.8%       | 6.0%                   |
| Cardiovascular diseases     | 13.2%       | 22.9%\(\Delta\)        |
| Other, mainly respiratory diseases | 6.6%   | 6.4%                   |

*Excluding patients who are alive or have died from unknown causes.\(\Delta\)Not statistically significant.
managed usefully according to the results of the National Prostatic Cancer Project. The National Prostatic Cancer Project participants (see box on page XX) have demonstrated that a variety of forms of chemotherapy in such patients who have had previous radiotherapy or who have not been treated with radiotherapy, can be effective in controlled randomized clinical T values. Although these agents are toxic, under a carefully controlled program they can be used successfully. Their results have been documented.\textsuperscript{20-22} It is important to emphasize that the criteria and evaluation of the response parameters selected by this particular national group have been found reproducible and useful in the hands of others.\textsuperscript{23} Moreover, they too, even in dealing with widespread metastatic disease in patients who have relapsed after all forms of conventional therapy, have found a relationship between primary tumor histologic grade and the response to chemotherapy.\textsuperscript{24} This im-
important viewpoint will be pursued and further studied. In addition to the ability of these new treatments to provide an alternative for the relief of pain, other objective and measurable partial responses have been observed. Some of these were first described in 1973 in terms of an agent, and further follow-up has now shown this to be true of still others. 23 Steroidal complexes combined with chemotherapeutic agents do have direct effects on human prostate cancer. 30 Phase I and cures, it will also assure the quality of life and the maintenance of our high clinical standards. In the very near future, adjuvant chemotherapy in patients with positive periaortic nodes or other advanced stages of surgical disease will be undertaken, expanding parameters and knowledge. This is the basis for reasonable and justifiable optimism and may well produce future reports from the National Cancer Institute reflecting improvement in survival rates for greater durations and for larger numbers of patients. It is unfortunate and regretful that we cannot separate our goal of primary therapy from that of palliative therapy. On the one hand we must have a concern for the welfare of our patients 30 but this should be tempered with the realization that many require treatment and many present with advanced prostate cancer despite our current highly developed medical facilities and technology. 31 This, however, can be altered as demonstrated by the alternatives of chemotherapy.

We are defining metastatic disease in new ways: it is being defined by surgical intervention, by lymphangiogram and by

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Phase II trials currently underway will provide opportunities to develop alternatives. As a result of this interest in extensive disease, patients with metastatic prostate cancer at various sites other than bone are now receiving careful clinical evaluation and the assessment of their measurable responses is being documented. 27, 28 It is recognized that chemotherapy in the advanced stage of disease will not be the final answer but rather an alternative to treatment which already has proved useful and at this point justifies our earlier optimism in 1973. 29

Future Perspectives

Combination chemotherapy of selected agents and other new single agents has been proved active under national randomized trial conditions. Under this affordable and desirable parameter, patients newly diagnosed, or those with stable stage D prostate metastatic cancer, are being afforded the opportunity for treatment with these drugs. The studies are underway and will take some time before complete evaluation. At no time in their conduct will the patient be denied an opportunity for exposure to conventional or hormonal therapy. While this may complicate the evaluation of possible chemotherapy

other external means to a degree never done before. As a result, we have larger numbers of patients at an earlier phase of their disease, compared to the early 1970's. Multidisciplinary treatment remains most important; so-called surgical staging, urological operative intervention and radiological treatment have established their abilities to provide significant and substantial improvements in survival of primary tumors. Hormonal palliation is still a mainstay and will unquestionably remain so for the future. The role of adjuvant chemotherapy has, since 1973, progressed to the point of being appropriately considered for controlled trials in those

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patients with early diagnosed, microscopic, occult or progressive disease. Comparing their results with palliative therapy will be a fruitful endeavor and should provide us with a basis for optimism and hope.

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