Urologic Oncology

Cancer Treatment and Research

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Urologic Oncology

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Foreword

Where do you begin to look for a recent, authoritative article on the diagnosis or management of a particular malignancy? The few general oncology textbooks are generally out of the date. Single papers in specialized journals are informative but seldom comprehensive; these are often preliminary reports on a very limited number of patients. Certain general journals frequently publish good indepth reviews of cancer topics, and published symposium lectures are often the best overviewes available. Unfortunately, these reviews and supplements appear sporadically, and the reader can never be sure when a topic of special interest will be covered.

Cancer Treatment and Research is a series of authoritative volumes which aim to meet this need. it is an attempt to establish a critical mass of oncology literature covering virtually all oncology topics, revised frequently to keep the coverage up to date, easily available on a single library shelf or by a single personal subscription.

We have approached the problem in the following fashion. First, by dividing the oncology literature into specific subdivisions such as lung cancer, genitourinary cancer, pediatric oncology, etc. Second, by asking eminent authorities in each of these areas to edit a volume on the specific topic on an annual or biannual basis. Each optic and tumor type is covered in a volume appearing frequently and predictably, discussing current diagnosis, staging, markers, all forms of treatment modalities, basic biology, and more.

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Where can you go find quickly a recent authoritative article on any major oncology problem? We hope that Cancer Treatment and Research provides an answer.

WILLIAM L. MCGUIRE
Series Editor

Preface

The ultimate goal of laboratory and clinical research in the field of uro-oncology is the cure of genitourinary malignancies. The primary objective of *Urologic Oncology* is to critically review recent advances in clinical and laboratory research that may impact on the cure of genitourinary malignancies. The chapters in this textbook were written by recognized authorities in uro-oncology. We are grateful for the outstanding manuscripts submitted by the contributors.

The cure of genitourinary cancer is directly related to the stage of the neoplasm at the time of the presentation. Therefore, 'early detection' of genitourinary malignancies will favorably impact on the survival rates of affected individuals. The role of transrectal prostatic ultrasound for the early detection of prostate cancer is very controversial. The efficiency of transrectal prostatic ultrasound as a useful study for screening or early detection of adenocarcinoma of the prostate is critically reviewed.

Surgery alone will cure a select group of individuals with adenocarcinoma of the prostate, nonseminomatous germ cell tumors (NSGTC), squamous cell carcinoma of the penis, and Wilms' tumor. The role of radical prostatectomy, radical retroperitoneal lymphadenectomy, penectomy and inguinal lymphadenectomy, and radical nephrectomy for the treatment of the above-mentioned neoplamds is controversial. The role of surgery for the treatment of prostate cancer, NSGTC, squamous cell carcinoma of the penis, and Wilms' tumor is critically examined.

The relative efficacy of therapeutic alternatives for the treatment of genitourinary neoplasms is dependent upon the achievement of cure, prolongation of survival, impact on the quality of life, and the morbidity of treatment. During the past decade, surgical procedures for genitourinary malignancies have been modified in order to diminish the morbidity of treatment without compromising the effectiveness of the cancer operation. The nerve-sparing modifications proposed by Walsh are associated with preservation of potency in 70% of men undergoing radical retropubic prostatectomy. Radical retroperitoneal lymphadenectomy can be performed with the preservation of ejaculatory function in 90% of men with Stage I NSGTC. Continent urinary diversion and orthotopic bladder replacement using intestinal segments represents

reliable alternatives for cutaneous urinary diversion following cystectomy. Laser treatment of superficial transitional cell carcinoma of the bladder is presently offered as an outpatient procedure. These modifications have altered the role of surgical intervention for the treatment of genitourinary malignancies. The impact of these therapeutic modifications are discussed.

Genitourinary malignancies that are not organ confined are rarely amenable to cure by surgical extirpation. The impact of chemotherapy on the survival of individuals with Wilms' tumor and NSGTC is well recognized. The survival rates for the remaining genitourinary tumors have not changed appreciably over the past decade. Recently, effective chemotherapeutic regimens have been reported for the treatment of invasive transitional cell carcinoma of the bladder. The status of chemotherapy for invasive transitional cell carcinoma is reviewed.

Laboratory studies that may impact on future therapeutic modalities are also discussed. The potential use of adoptive immunotherapy in the form of interleukin-2 and lymphokine activated killer cells; heterogeneous composition of tumors; stromal-epithelial interaction in the development, maintenance, and growth of the prostate; and the mechanisms by which intravesical bacillus calmette-guerin mediates antitumor activity are discussed.

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1. Prostatic ultrasound for the early detection of prostate cancer

ALAN ANGELL and MARTIN I. RESNICK

In 1988 it is estimated that 99,000 men will be diagnosed as having adenocarcinoma of the prostate, an incidence equal to lung cancer and comprising 20% of all male malignancies. The estimate for the death rate is 11% of all male neoplasms, second only to colorectal cancer and immediately behind lung cancer. Since 1970, the age-adjusted death rate for carcinoma of the prostate has been on the rise and is now 22 per 100,000 men per year, and in 1988 approximately 25,500 men will have died from the disease [1].

While the death rates are high, not all men diagnosed with prostate cancer will die as a consequence of the disease. Many of these malignancies are subclinical and only discovered incidentally or at autopsy. Five to forty percent of men (depending upon various estimates) over the age of 50 have histological evidence of carcinoma of the prostate, which may be more indicative of the true prevalence of this disease. The discrepancy between the high prevalence rate and the mortality rate may be due to several factors, including biologically nonaggressive disease, early detection, better treatment, and/or death from other causes. [2]. As the population ages and the post-war 'baby boomers' reach maturity, it can be expected that the actual number of cases of prostate cancer will rise, which will likely be associated with significantly greater morbidity and mortality.

As with other types of malignancies, efforts are underway to diagnose prostate cancer at an earlier, and hopefully curable, stage. Screening for cancer must be differentiated from early detection. Screening implies that all individuals in a specified group at risk (e.g., men over the age of 50) are evaluated on a regular basis. Early detection of a disease process assumes that the patient develops a new sign or symptom that alerts the patient and/or physician that a problem may exist, which initiates the evaluation. With prostate cancer, this may include a change in voiding pattern, hematuria, or a palpable nodule detected on routine digital rectal examination.

Through projects of various health organizations, physicians, and other health care specialists and the media, the public has been made increasingly aware of cancer and that it can be cured if detected early. It has also been repeatedly emphasized that patients can and should be partly responsible for their own welfare. Coupled with a population that is now, more than ever,

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concerned about its health, are advancements in medical technologies. These areas, such as imaging, clinical chemistry, and invasive tissue sampling, hopefully will allow for diagnosis at an earlier stage in both the asymptomatic and/or symptomatic patient.

The debate on how and when to use these methods is not new, nor is it limited to prostatic cancer. When devising a methodology, factors such as cost, benefit, risk, morbidity, and feasibility for use on a mass scale need to be studied. These data are usually collected from epidemiological studies that involve large groups of patients. For example, mammographic screening for breast cancer has been a topic of debate for many years. A recent study examined routine mammograms in breast cancer screening for women under 50 years of age. The benefits of early discovery were weighed against the risks such as: unnecessary biopsies because of falsely positive studies, the false sense of security because of a falsely negative study, the small risk of developing cancer from radiation, unnecessary disfigurement, morbidity and mortality from surgery and anesthesia, and financial costs for the study, surgery, and pathology. In addition, it has been emphasized that with health care resources becoming increasingly scarce, money saved from screening could be used for research in both prevention and cure [3]. After compilation of data from the study, it was recommended that women less than 50 do not undergo routine mammographic screening (unless they are at increased risk, e.g., strong family history) because the benefits do not outweigh the risks. [3, 4]. In other areas of medicine, the benefits far outweigh the risks. For example, screening for occult fecal blood is economical, without morbidity, and rapid.

Many approaches have been tried in an attempt to detect prostatic cancer at an early stage. Among these include the digital rectal examination, analysis of shed cells in urine, measure of levels of prostate proteins in the serum, and various imaging techniques. Among the imaging modalities, magnetic resonance imaging (MRI) and computerized tomography (CT) have found little use in screening and early detection of prostate cancer. MRI cannot reliably differentiate malignant from benign disease, however, it is accurate for staging purposes. It is also very expensive, which makes its use as a screening study impractical. CT scanning as well has only been found useful for detecting invasion or gross lymphadenopathy. It cannot detect lesions confined to the prostate because benign and malignant processes have the same attenuation coefficients. MRI and CT both have low sensitivities and therefore cannot be used to detect early disease [5].

Digital rectal examination

Digital rectal examination of the prostate is considered the gold standard against which other methods for early detection are compared. In 300 at-risk patients (ages 50–90 with symptoms of obstruction), rectal exams were by far

the most sensitive method for detection of carcinoma. The prevalence rate was found to be 0.23. While rectal examinations had the highest sensitivity and a high specificity, other tests such as enzymatic determination of acid phosphatase had a higher specificity. Overall, the rectal examination had the highest efficiency of detection of disease, and 'in a population with a higher prevalence of disease, the sensitivity of a test contributes relatively more to overall efficiency than its specificity does' [6].

Using a different approach, Chodak and associates performed digital rectal examinations and transrectal ultrasound studies in 216 men. [7]. Biopsies were only performed if there was an abnormal finding upon digital examination. Eighty-eight patients underwent biopsy and 28 of these men were diagnosed as having carcinoma. The sensitivity for ultrasound among these diagnosed afterwards was 86%, but the specificity was only 41%. The positive and negative predictive values were 36% and 89%, respectively. Based on this experience, the authors concluded that suspicious lesions on ultrasound should be biopsied. They did not recommend routine screening in the United States because of the low positive predictive value obtained with the study. One more important factor appeared to be that the ultrasound examination itself was very operator dependent. The interpretation of the scans appeared to be dependent upon the experience of the operator, and the sensitivity fell considerably when performed by urologists with less than 2 years of experience. The investigators did not indicate how many isoechoic tumors would have been missed on the ultrasound study.

Thompson et al. originally concluded that the digital rectal examination was a relatively poor method for detection of prostate cancer. In a review of 2005 men over the age of 40 with palpable abnormalities, 43% of those with benign biopsies were symptomatic, whereas only one patient with biopsy-proven carcinoma had any symptoms. In patients who were biopsy positive, 66% were upstaged from localized to invasive or metastatic disease after surgical staging. They noted on biopsy that the ratio of benign to malignant palpable abnormalities was 4:1. Furthermore, because of the 20–25% chance of a patient having stage A carcinoma, a significant number of lesions would have been missed on rectal exam. Symptoms could not be relied upon for early detection because of the very small percentage of men who were symptomatic and had carcinoma [8].

More recently Thompson has reversed his thinking on digital rectal examination for purposes of screening. Even though 60% of malignancies found by digital examination were upstaged, the examinations increased the detection of clinically localized early carcinomas. Based on this experience, they recommended routine yearly screening by digital rectal examination in men over 50 years of age as an inexpensive, noninvasive method that any properly trained physician could perform. Their studies showed that routine screening increases the probability of finding a carcinoma in an earlier clinical stage. [9].

In another screening program using digital rectal examinations, 43 abnor-

mal examinations were found in 811 men over the age of 45 [10]. Thirty eight of these lesions were biopsied and 11 were found to be carcinoma. The incidence of carcinoma in this population was found to be 1.7%. The cost of finding each tumor was $6300, compared with $8500 for cervical cancer and $28,000 for breast cancer. [10]. Cuinan has also recently reaffirmed his thinking that the digital rectal examination is more efficient than transrectal ultrasound, prostatic acid phosphatase, prostate-specific antigen, and aspiration cytology [11].

Ultrasonography

Ultrasonography of the prostate was first popularized by Watanabe and has been found to also be a sensitive screening study [12]. Several different routes have been tried to examine the prostate, and these include transabdominal, transurethral, transrectal, and transperineal scanning. The transrectal method has, for a variety of reasons, become the best way to both reliably and reproducibly image the prostate. Transurethral imaging is painful and requires a regional or general anesthetic. Transperineal scanning was used primarily for research interest [13], and the transabdominal approach has great variability between exams. It does not provide sufficient detailed information regarding the internal architecture of the prostate, and the apex is poorly visualized [14].

Upon transrectal ultrasound examination, the normal prostate has a well-defined, highly echogenic capsule that is continuous and symmetrical (Fig. 1). In benign prostatic hyperplasia, the gland is diffusely enlarged, appears rounder than the triangularly shaped normal prostate, and has a thickened capsule (Fig. 2). The many fine echoes seen in the interior represent small adenomata [15]. Increased echogenicity is seen with chronic prostatitis and calculi [16]. Calculi may also exhibit acoustical shadowing, as seen with calculi elsewhere in the body. The seminal vesicles are cephalad and have less echogenicity than the prostate; they should appear as symmetrically placed, equally sized structures [13].

The ultrasound characteristics of carcinoma of the prostate has undergone significant change in concept over the past 2–3 years and has become an area of controversy. There is almost uniform agreement that advanced carcinoma causes gross distortion of the prostate, with loss of capsular contour and symmetry (Fig. 3). The seminal vesicles will often be distorted or lose their hypoechoic appearance if invaded [13]. Due to tumor spread and invasion, advanced lesions tend to have a heterogeneous appearance, with a mixture of hyperechoic and hypoechoic areas [17]. Echoes are believed to be caused by the interfacing of tissues of different densities [18], and their hyperechoic nature is caused by invasion of the stroma. Additionally, the desmoplastic reaction often associated with advanced tumors is believed to contribute to this pattern. If the capsule is invaded, there will be loss of its symmetry and

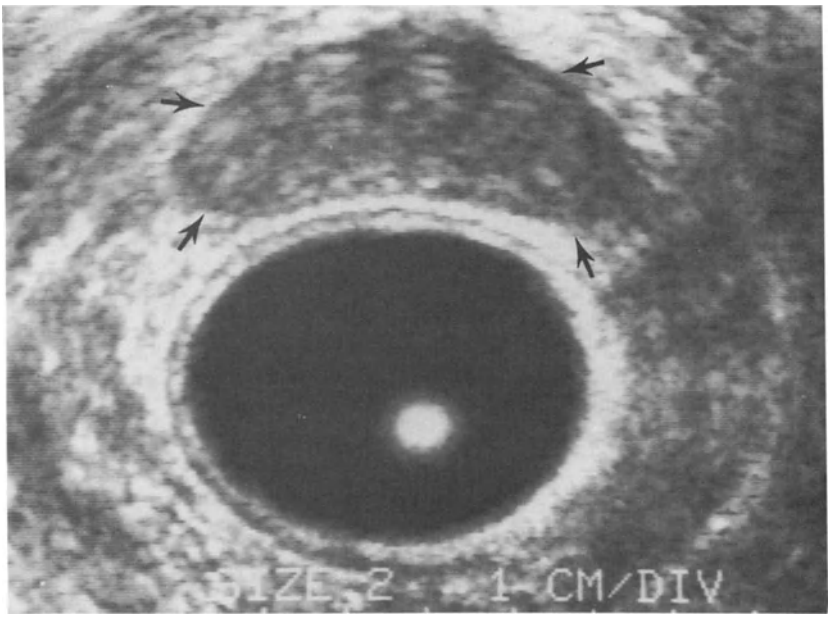

Figure 1. Transrectal scan of normal prostate. Arrows depict prostate capsule.

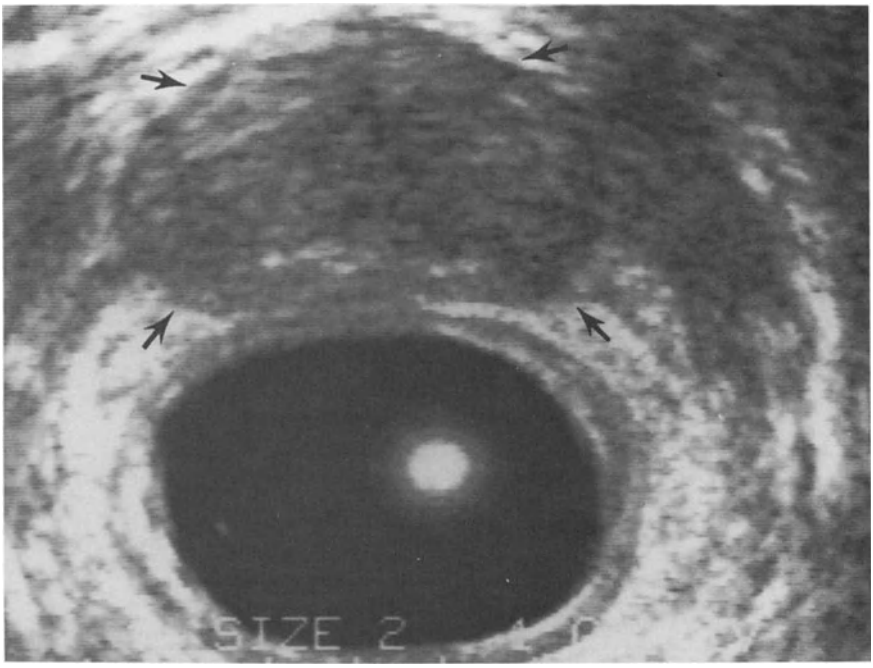

Figure 2. Transrectal scan demonstrating change of benign prostatic hyperplasia. Arrows depict prostatic capsule.

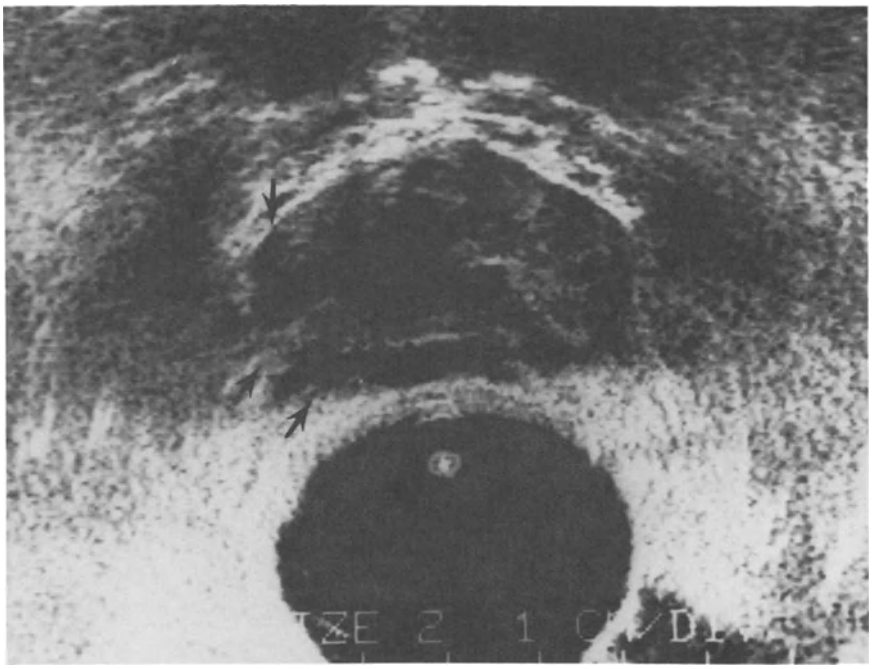

Figure 3. Transrectal scan demonstrating changes of invasive carcinoma of the prostate. Arrows depict region of capsular disruption.

well-defined limits — the capsule becomes blurred and there is a loss of distinction from the surrounding tissue [13].

Localized prostate cancers were at first believed to have increased echogenicity when viewed ultrasonically. With the use of newer instruments, and particularly higher frequency transducers, it became evident that some, particularly the smaller tumors, may have a mixed or decreased echogenicity [19] with 77% echogenic and 23% of mixed echogenicity [20] (Fig. 4). Because of the inability of ultrasonography to reliably distinguish benign from malignant disease, it has long been thought that prostatic ultrasonography was not useful as a screening test for prostatic cancer. Studies have shown the examination to have a high sensitivity of over 90%, but a low specificity varying between 40% and 60%. Half of the abnormalities first believed to be prostate carcinoma were due to benign adenomatous disease, calculi, or prostatitis [15, 21, 22].

It is important to understand that just because a modality (ultrasonography, digital rectal examination, tumor markers, etc.) has a high sensitivity does not necessarily imply it is applicable for a mass screening program. A sensitivity of 90% means that 90% of patients with a given disease have a truly positive test, not that 90% of all patients with a positive test have the disease. This second phrase represents the positive predictive value and takes

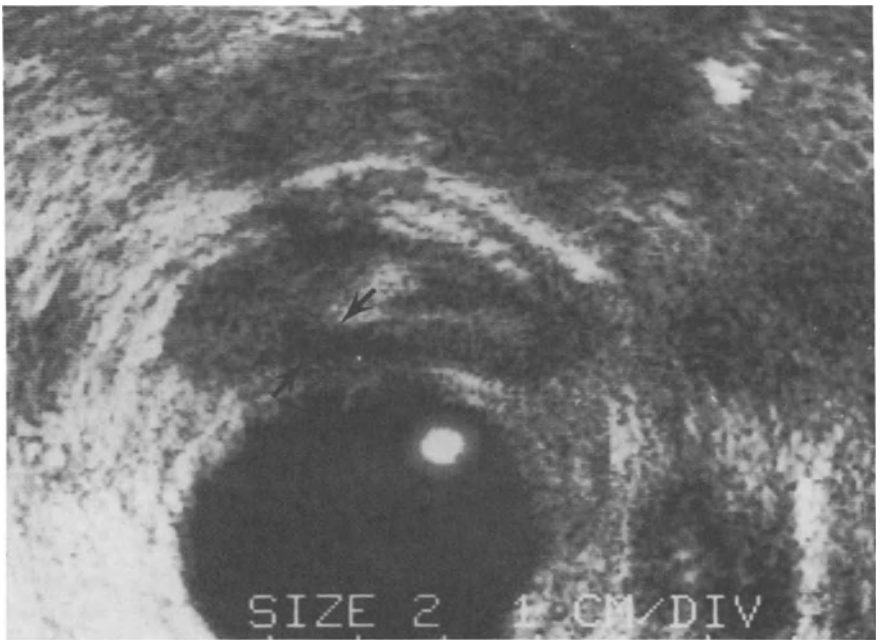

Figure 4. Transrectal scan demonstrating changes of localized carcinoma of the prostate. Arrows depict hypoechoic peripheral abnormality.

into account test sensitivity and specificity, and disease prevalence in the population being studied. For example, the radioimmunoassay-determined prostatic acid phosphatase was initially thought to be useful for mass screening until the positive predictive value was computed (the sensitivity was 70%, the specificity was 94%, and the disease prevalence was 35 in 100,000 — the positive predictive value was 0.19% for stage A prostate carcinoma — one man in 526 with a positive test and no palpable nodule had stage A disease) [23].

In an effort to increase the specificity of the study, several criteria of ultrasound have been examined. Rifkin et al. evaluated the echo brightness and thickness of the internal echoes to try to separate malignant from benign processes. On specimens obtained from both needle biopsies and transurethrally resected tissue, over one half of all benign tissue specimens were as echogenic or more echogenic than the capsule. Thirty-two precent of benign disease had an echo brightness between that of normal prostate and capsule. Overall, malignant lesions had somewhat less echo brightness than benign disease. However, there was too much overlap of the criteria, and echo thickness and brightness were not useful as markers to reliably separate malignant from benign disease. The investigators could only conclude that ultrasound imaging had a 96% ability to detect focal abnormalities [24].

As research continued, some investigators began to question whether the

pathological specimens obtained by needle or transurethral resection truly represented the abnormality thought to have been imaged. Did the areas of altered echo returns actually correlate with disease? To answer the question, two groups of investigators looked at whole-mount specimens obtained following radical prostatectomy or autopsy, and correlated the histological patterns with the ultrasound findings. In one series, patients were scanned before radical retropubic prostatectomy, and the specimens were again scanned after removal. Assessment of the data revealed that 54% of carcinomas were echopenic, 22% slightly hypoechoic, and 24% isoechoic (unable to be identified on ultrasound) [14]. The other group of investigators obtained specimens at the time of autopsy. Of 100 cadaveric prostates, 26 were found to have carcinoma. Of these, 73% were hypoechoic, 12% isoechoic, and 15% hyperechoic. In the 13 glands without capsular invasion, 54% were hypoechoic, 23% were isoechoic, and 23% hyperechoic [25]. Earlier work from the same group had originally described the areas of carcinoma as heterogeneous on ultrasound [26].

Using the concept that hypoechoic lesions signify carcinoma, Lee et al. have become proponents of routine biopsy if these areas are detected. Based upon work by McNeal that divides the prostate into central transition and peripheral zones [27], Lee initially stated that occult disease begins in the posteriorly located peripheral zone. This region is amenable to examination by transrectal ultrasonic imaging. In a group of 417 men, aged 29–96 (mean age 63 years), transrectal ultrasonography led to needle-guided biopsy in 45 men who had abnormalities visualized. Of the eight patients who had hyperechoic centrally located lesions biopsied, histological study revealed only benign disease in all instances. Twenty-two of the 32 satisfactory biopsies of peripherally located hypoechoic areas were reported as positive for malignancy [28]. In another series of 80 patients who underwent biopsies of peripheral hypoechoic areas, 53% were reported as cytologically positive, while 54% were histologically positive, for a combined yield of 61%. However, 56% of these patients had discrete findings upon rectal examination, while 24% had equivocal findings, leaving only 20% with a normal digital rectal exam.

Of those patients with positive biopsies, Lee reported that 57% of lesions less than or equal to 1.5 cm were not palpable or equivocal upon rectal examination [29]. However, assessment of the data reveals that only 10% of hypoechoic lesions identified on ultrasound as carcinoma and biopsy-proven to be so were nonpalpable. Thirty-one percent were 'equivocal' upon digital exam. Furthermore, the false-negative rate is unknown, as hyperechoic lesions were not biopsied, and there is no way to differentiate isoechoic lesions from normal or benign surrounding tissue.

In an attempt to further define the issue, Lee has devised an ultrasound staging system that has been modified from the standard Whitmore classification system. Under this system, most lesions that an ultrasound appear to be impalpable are actually either palpable or equivocal by examination [30]. Additionally, a lower percentage of these smaller hypoechoic lesions on

ultrasound are positive on biopsy. Only 25% of lesions less than or equal to 1.5 cm are positive on biopsy, while 96% of lesions greater than 1.5 cm are palpable. It must also be emphasized that one must be cautious when trying to equate tumor volume as determined by ultrasound with the true histological pattern of the malignancy. Though limited data exists, experience suggests a poor correlation, particularly when the tumors are located more anteriorly. Additionally, 30–50% of tumors are isoechoic and cannot be visualized with this modality.

The value of ultrasound for screening or early detection of prostate cancer has become a topic of debate. In 1981, Resnick reviewed the usefulness of ultrasound in screening and concluded that transrectal ultrasonography was poor in screening for prostate cancer because of the low specificity and sensitivity [13]. Although a small number of nonpalpable neoplasms could be detected with ultrasound, many could not. The false-negative rate may be attributable to A_2 disease, which may not be detectable because of the lack of an interface between benign and malignant tissue. This interface is necessary for the return of echoes to the transducer head.

Lee has advocated that routine screening of the prostate by transrectal ultrasound will complement the digital rectal examination. Improvements in equipment, such as in higher frequency transducers, have enabled better visualization of the prostate, particularly of the posterior peripheral area. The premise that all carcinomas develop in the peripheral zone of the prostate was the primary basis of this belief. Normally this tissue is homogeneous and early lesions, which are often hypoechoic, will be clearly identified. As carcinomas enlarge and invade, they too can develop a hyperechoic appearance and appear similar to benign disease [31].

Cooner et al. performed ultrasound examinations on 415 men, 225 of whom had periodic digital rectal examination for at least 2 years. Patients ranged in age from 50–89 years. None of the men were believed to have abnormalities upon examination necessitating biopsy. Ninety-six (42.7%) of these men underwent biopsy of an abnormal area as determined by ultrasound. Carcinoma was found in 28 specimens, 29.2% of all lesions biopsied or 12.4% of all men believed to have benign findings on digital rectal examination. Of these 28 men, only 12 were treated with radical prostatectomy or radiation therapy. Two had stage D2 disease and required orchiectomy, three could not be treated because of advanced age and/or poor health, and 11 were under evaluation and staging at the time of the report. Based on this experience, it was recommended that all men over 50 years of age should undergo a baseline rectal exam, prostate-specific antigen (PSA) level, and transrectal ultrasound. Routine reexamination was not recommended, but the former studies should be repeated yearly. Any patient with an abnormality that became palpable or the development of an elevation in PSA should automatically undergo ultrasound and biopsy of any suspicious areas [32].

The preceding studies are difficult to place in perspective when advocating or refuting routine ultrasound for screening or early detection of adenocar-

cinoma of the prostate. In one series, the age range of patients was from 29 to 96 years. Some patients had symptoms or palpable abnormalities, while others did not. As noted, many with diagnosed disease could not be treated because of associated medical problems or advanced age.

Experience has shown that transrectal ultrasonography is also unable to adequately scan the anterior portion of the prostate. The newer high-resolution, high-frequency probes do not have enough power to overcome energy losses in tissue, and hence the resolution for the anterior part of the gland has been found to be poor. Furthermore, in contradistinction to Lee's theory and his own initial beliefs based on histologically examined radical prostatectomy specimens, McNeil observed that stage A carcinomas were located anteromedially [33]. Even when these carcinomas became large, they tended not to spread too close to the rectal surface. As previously recognized, stage B carcinomas were located posteriorly. The only difference between stage A and B carcinomas was their location and not the aggressiveness of the tumor. Twenty-seven percent of the carcinomas in this series were undetectable by digital rectal examination [33]. This data must be interpreted in view of the findings of Lee that early carcinomas are found posteriorly. As discussed previously, anterior stage A lesions usually cannot be detected by transrectal ultrasound examination and a UAl lesion (Lee classification confined to the prostate, <1.0 cm on ultrasound) [30] may not correlate with a stage A_1 pathological lesion but could possibly indicate diffuse disease that began in the anterior tissue.

Other considerations must also be taken into account when transrectal ultrasonography is performed. If a lesion is biopsied, there is a risk of bleeding, infection, urinary retention, sepsis, and death with this supposedly 'benign' procedure. Additionally there are the added costs of performing the examination, interpretation costs, equipment costs, and lost time to patients. Routine screening could cost millions of health care dollars a year. Although this is not advocated, it may be cheaper to not perform ultrasound but just randomly biopsy prostates that are palpably normal. One hundred and two men with palpably benign prostates underwent pretransurethral resection, four-quadrant aspiration biopsies. While stage A_1 carcinoma was not detected, when adequate material was obtained all stage A_2 carcinomas were detected on aspiration [34]. This report only emphasizes the concept that the more one biopsies a prostate, regardless of the method or techinque, the more cancer will be detected.

To date, no randomized trial has been performed to evaluate the efficiency of transrectal ultrasound as a useful study for screening or early detection for adenocarcinoma of the prostate. Many of the studies described in this chapter are anecdotal and have involved mixed groups of asymptomatic and symptomatic patients of varying age ranges, including patients without and with palpable abnormalities, as well as patients self-referred. Additionally, what requires evaluation during any screening study are the frequency of examinations, as well as the age groups and other risk categories that need to

be included or excluded. While transrectal ultrasound of the prostate is useful in staging patients once the diagnosis has been established [5], it should not be used for purposes of screening or early detection of adenocarcinoma of the prostate until these questions can be resolved by large, randomized trials.

Furthermore, once occult lesions are found and proven to be carcinoma by biopsy, what should be done with these patients? The natural history of men with stage A_1 lesions is not well known, and not all of these cancers would necessarily become clinically evident during a patient's lifetime. It is not unreasonable to believe that if all men with carcinoma of the prostate were detected and treated, the morbidity and mortality of this intervention may be greater than the morbidity and mortality of this disease itself. Stamey noted several years ago, ' .... that for every male who dies of prostate cancer each year, there are hundreds who have the disease without symptoms and the doubling time of prostatic cancer cells must be so slow that, at least in most instances, many years are required for the cancer cells to reach the critical metastatic volume within the prostate to cause death from metastases.' [35]. In one study, 16% of men with untreated stage A_1 disease moved on to progression 8 or more years after the time of original diagnosis was made [36]. In another series, one quarter of the patients moved on to progression after a mean of 11.5 years [37]. The problem is to try to identify which of these lesions wil progress. More patients will die of unrelated causes than will develop progressive disease [38]. As Dr. Willett Whitmore stated, 'Is cure necessary? Is cure possible? Is cure possible only when not necessary?' [39].

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2. The Role of Radical Prostatectomy in the Treatment of Cancer of the Prostate

HERBERT LEPOR

Radical prostatectomy: Historical perspective

Radical perineal prostatectomy was originally described by Kuchler in Germany in 1866 [1]. Hugh Hampton Young modified the perineal approach to radical prostatectomy by making the operation more anatomical and practical [2]. Young's original technique was associated with urinary–incontinence in approximately 50% of cases [3]. The surgical approach to radical prostatectomy has undergone many additional modifications and refinements. Vest described a technique for approximating the bladder to the urethra so that tension would be taken off the external sphincter [4]. The anastamosis was performed using mattress sutures placed anteriorly and laterally. Jewett further modified the anastamosis by substituting simple sutures for Vest's mattress sutures and by providing a mattress suture that approximated the anterolateral bladder wall to the urethra [4]. The water tight anastomosis of the bladder and urethra decreased the incidence of incontinence and anastomotic strictures.

The retropubic approach to radical prostatectomy was introduced and popularized by Millin in 1947 [5]. Urologists have turned to the retropubic approach for radical removal of the prostate because of the lack of familiarity with the anatomy of the male perineum and increased experience with pelvic surgery. A major advantage of the retropubic approach is that a staging pelvic lymph node dissection is performed immediately prior to the prostatectomy [6]. Although proponents of the perineal approach have emphasized the advantages offered by the direct approach to the prostate and the ease of performing the urethrovesical anastomosis, the retropubic approach has become the more widely accepted approach to radical prostatectomy.

Jewett was the first surgeon to report the surgical complications of a large consecutive series of men undergoing radical prostatectomy [3]. A single postoperative death occurred in the 103 consecutive cases reviewed. Four anterior rectal injuries were primarily repaired and healed without fistula formation. Thrombophlebitis occurred in two patients. Complete urinary continence was observed in 80/82 cases. Impotence was observed in 90% of

Lepor H. and Ratliff T.L. (eds), Urologic Oncology.

the men. Several surgeons have subsequently reported more recent reviews of radical prostatectomy for carcinoma of the prostate [7–12] (Table 1).

Overall, radical prostatectomy is associated with limited operative morbidity and mortality (Table 1). Nevertheless, the development of impotence limited the widespread acceptance of radical prostatectomy for the treatment of prostate cancer. The factors causing impotence following radical prostatectomy were not recognized until Walsh and Donker described the pathway for the autonomic innervation of the human corpora cavernosa in fetuses and stillborn male neonates [13]. Based upon anatomical observations made from these dissections, it was hypothesized that the autonomic innervation to the corpora cavernosa was injured during ligation of the inferior vesical pedicles, mobilization of the urethra, and incision of the lateral pelvic fascia. Walsh et al. subsequently described the nerve-sparing radical retropubic prostatectomy, emphasizing the following modifications in order to preserve the autonomic innervation to the penis: The infravesical pedicle is divided immediately adjacent to the prostate; the lateral pelvic fascia is incised anterolaterally, and the urethra is mobilized immediately adjacent to the adventitia of the urethra [14]. Potency was preserved in 10 (83%) of the first 12 men undergoing nerve-sparing radical retropubic prostatectomy. The validity of these nerve-sparing modifications were supported by a detailed anatomical study of the human male pelvis performed by Lepor and associates [15]. A detailed pathological review of the first 100 consecutive surgical specimens have demonstrated that the adequacy of the cancer operation is not compromised by the nerve-sparing modifications [16]. In fact, pathological studies have indicated that the surgical margins achieved during nerve-sparing radical retropubic prostatectomy are better than achieved following radical perineal prostatectomy [14].

Historically, advocates of a nonsurgical approach to carcinoma of the prostate have emphasized the excessive intraoperative and post-operative morbidity associated with radical prostetectomy. Radical prostatectomy at one time represented the only curative treatment for organ-confined disease. Radiation therapy, administered as intracavitary radium treatments, was introduced for the treatment of prostate cancer in 1915 by H. H. Young [17]. The definitive use of external beam irradiation was first described by Holtberg in the 1940s [18]. Radiotherapy gained more widespread acceptance than radical prostatectomy, since impotence was not a recognized sequelae of radiotherapy and the immediate and late side effects of radiotherapy were perceived as negligible. The impact of radiotherapy on erectile dysfunction has only recently been appreciated. The development of impotence following radiation therapy ranges between 22% to 84% [19–23]. Goldstein et al. recently observed that after radiation therapy, 15 (79%) of 19 men who were previously potent or who had partial erections complained of an adverse change in erectile function [24]. Radical prostatectomy is offered with the virtual assurance of preserving urinary continence and the expectation of preserving potency in the majority of men. Radical prostatectomy performed

Table 1. Complications following radical retropubic prostatectomy

	Kopecky et al. 1970 [7]	Middleton 1981 [8]	Lieskowsy 1983 [9]	Crawford et al. 1983 [10]	Igel et al. 1987 [11]	Lepor and Walsh 1987 [12]
Number of patients	73	50	65	75	692	290
Mortality	0%	0%	1.5%	0%	0.6%	0%
Intraoperative complications						
Rectal injury	1.4%	2%	3%	0%	1.3%	0%
Ureteral injury	1.4%				0.3%	0.3%
Early complications						
Thrombophlebitis	6.9%	12%	3%		1.2%	0%
Pulmonary embolus	2.7%	2%	4.6%		2.7%	1.0%
Wound infection	16%		3%	5%	1.0%	
Lymphocele		2%	3%		0.9%	
Urethrovesical dehiscence	4%		1.5%		0%	0%
Late complications						
Contracture of bladder neck	12%	6%		2.6%	5.4%	
Incontinence	1.4%	4%	3%	1.3%	5.0%	
Impotence	91%	100%				

by experienced surgeons familiar with the nerve-sparing technique represents the least morbid therapeutic option for the treatment of organ-confined prostate cancer.

Indications for Radical Prostatectomy

Radical prostatectomy has been advocated for the treatment of virtually every stage of prostate cancer. The indications for radical prostatectomy should reflect an understanding of the natural history of the disease, the projected survival of the patient, the stage of the disease at presentation, and the relative morbidity and efficacy of alternative therapeutic options. The natural history of prostate cancer remains poorly understood. A series of untreated men with localized cancer of the prostate with long-term follow-up has not been reported in the literature. The relative morbidity and efficacy of alternative therapeutic regimens for the treatment of carcinoma of the prostate are essentially unknown, since randomized clinical trials have rarely been performed. Comparative analysis of nonconcurrent studies are of limited value since staging criteria and statistical methods have not been standardized. It is therefore difficult to make definitive conclusions regarding the optimal treatment for any stage of carcinoma of the prostate.

Therapeutic intervention for carcinoma of the prostate is offered with the objective of achieving cure, local disease control, palliation of systemic metatases, and increased duration of survival. The cure of carcinoma of the prostate requires the complete excision or destruction of all malignant tumor cells. Hormonal therapy is a noncurative therapeutic modality, owing to the development of hormone-resistant tumor cells [25]. An effective chemotherapeutic regimen has not been developed for the treatment of carcinoma of the prostate [26]. Owing to the limitations of hormonal therapy and chemotherapy, it is generally agreed that only carcinoma pathologically confined to the prostate is amenable to cure. Radical prostatectomy and radiation therapy represents the therapeutic options that are currently offered for the cure of organ-confined disease. The optimal curative treatment for carcinoma of the prostate represents one of the most controversial issues in urologic oncology [27]. Prostate cance that is truly pathologically confined to the prostate is cured following radical prostatectomy. The incidence of biologically active prostate tumor cells following definitive radiotherapy for clinically localized prostate cancer indicates that radiation therapy does not consistently achieve cure when the carcinoma is organ confined [28–30].

Radical prostatectomy may be offered with the objective of increasing survival for those men with microscopic or macroscopic tumor extending beyond the prostate. There is no evidence indicating that debulking the local tumor burden has a favorable impact on survival for men with carcinoma of the prostate. The impact of radical prostatectomy on survival rates for men with locally invasive disease will remain unknown until the natural history of

carcinoma of the prostate is clarified. A randomized clinical trial comparing survival rates following radical prostatectomy versus no treatment of stage C, stage D_0, and stage D_1 disease would clarify the value of radical prostatectomy for disease that is not pathologically confined to the prostate.

Prostate cancer is a well-recognized cause of bladder outlet obstruction in the aging male population. It is unlikely that prostate cancer associated with infravescial obstruction is amenable to cure. The symptoms of prostatism may be relieved following radical prostatectomy, definitive radiotherapy, transurethral resection of the prostate (TURP), and orchiectomy. The relative efficacy of these therapeutic options for local disease control has never been examined critically. Orchiectomy and TURP are associated with relatively minimal morbidity. Approximately 70% of men with stage D_2 disease and urinary retention void spontaneously and completely following orchiectomy [31]. It is unlikely that the morbidity of radiation therapy and radical prostatectomy justify their use soley for local disease control.

Radical prostatectomy: Stage A_1

Stage A prostate cancer refers to the detection of prostate cancer in surgical specimens removed from men undergoing prostatectomy for benign prostatic hyperplasia (BPH). Approximately 10% of prostatectomy specimens removed from men with symptomatic BPH will demonstrate pathologic evidence of adenocarcinoma [32–34]. Stage A prostate cancer can be subdivided according to extent and differentiation of tumor in the primary lesion [35–36]. Stage A_1 refers to well to moderately well-differentiated carcinoma (Gleason II–VII) involving less than 5% of the surgical specimen. Stage A_2 prostate cancer refers to any poorly differentiated carcinoma (Gleason VIII–X) or any tumor involving more than 5% of the surgical specimen. These criteria for subdividing stage A disease were established based upon a retrospective study at the Johns Hopkins Hospital of 117 untreated men with stage A prostate cancer [36]. In the initial analysis of these data, only 2% of patients with stage A_1 disease progressed, compared to a cancer progression rate of 33% among those patients with stage A_2 disease. However, in a more recent review of this series, 16% of 50 untreated men with stage A_1 disease traced for a minimum of 8 years have progressed [37]. Blute et al. have recently reviewed a series of men with stage A_1 disease who were conservatively managed at the Mayo Clinic and followed for a minimum of 10 years [38]. The likelihood of disease progression in this series was 27%.

The treatment of stage A_1 disease is exceedingly controversial. The assumption that stage A_1 disease represents a benign process is no longer valid. Unfortunately, the criteria has not been established for predicting those patients with stage A_1 disease predisposed to the development of disease progression [37]. Prostate cancer arises primarily from the peripheral component of the prostate [39–41]. A more extensive TURP is not likely to

ablate the residual tumor. It has been suggested that aggressive treatment should be reserved for those individuals who meet the criteria of stage A_2 disease following a repeat TURP [42–43]. There is no evidence indicating that patients upstaged following a repeat TURP are predisposed to the development of disease progression. Epstein and associates have recently reported the presence of residual carcinoma in 86% of radical prostatectomy specimens removed from men with stage A_1 disease [44]. It was the impression of the authors that the extent and location of the residual tumor precluded cure by repeat TURP. The residual carcinoma identified in these surgical specimens was pathologically confined within the prostate capsule.

The objective of therapeutic intervention for stage A_1 disease should be cure, since the natural history of stage A_1 disease is generally protracted and the tumor is virtually always pathologically confined to the prostate. An extensive repeat TURP is unlikely to completely remove the tumor residual. Hormonal therapy is unlikely to achieve cure owing to the presumed existence of androgen-insensitive cells. Radical prostatectomy and radiation therapy represent the therapeutic options available for cure of stage A_1 carcinoma of the prostate. The decision to offer definitive treatment must reflect the relative morbidity and mortality of treatment versus the disease process. The likelihood that stage A_1 disease will progress to metastatic disease within 10 years is approximately 20% [37–38]. There is no evidence indicative that the curve for disease progression plateaus at 10 years. The incidence of disease progression presumably will increase as the conservatively managed series are followed for longer intervals. The majority of men with disease progression will ultimately die of their malignancy, providing they do not succumb to other causes. The mortality rate following radiation therapy [45] and radical prostatectomy [7–12] for localized carcinoma of the prostate are less than 1%. The long-term survival rates following radical prostatectomy and radiotherapy for stage A_1 disease have not been determined. It is a reasonable assumption that the vast majority of men with stage A_1 disease are cured following definitive treatment. Epstein et al. have recently reported the preservation of continence and potency in 100% and 93% of consecutive men with stage A_1 disease undergoing radical prostatectomy [44]. Radical prostatectomy represents a very reasonable option for the healthy individual with stage A_1 disease and a life expectancy exceeding 10 years. The decision to proceed with definitive treatment for stage A_1 disease is controversial, and the decision should be made together with a well-informed patient.

Radical prostatectomy: Stage A_2 disease

Stage A_2 prostate cancer refers to any poorly differentiated cancer (Gleason grade VIII–X) or any tumor involving more than 5% of the resected or enucleated prostatectomy specimen [36]. The natural history of stage A_2

disease is the development of metastases in 33% of patients within 4 years [36].

Formerly, surgery for men with stage A_2 prostatic carcinoma was discouraged because it was believed that 1) secondary radical prostatectomy was difficult and rarely classical; 2) patients often had more advanced disease than previously recognized, thereby making cure unlikely; and 3) the incidence of incontinence and impotence in this setting was unacceptable [46]. However, based on recent data, patients with stage A_2 disease are ideal candidates for radical prostatectomy [47]. Secondary radical prostatectomy is no more difficult, and less often difficult, than in patients who have undergone needle biopsy of the prostate. Pathologic specimens removed at the time of surgery reveals that the vast majority have organ-confined disease (Table 2). Finally, using modern surgical techniques, most patients after radical prostatectomy are continent and potent. Previously, these patients were subjected to radiotherapy. Recently, it has been recognized that rectal injuries following external beam radiotherapy occur more frequently for men with stage A_2 disease. The increased incidence of rectal injuries is presumably related to the thin shelf of tissue that remains posteriorly after a transurethral resection. Major complications after external-beam irradiation are higher in stage A disease compared to stage B and C disease [48]. A recent series has indicated that 50% of the stage A_2 patients developed late major complications following radiotherapy [49].

It is presently impossible to evaluate the efficacy of radical prostatectomy for the treatment of stage A prostatic cancer. In most reported series, patients with stage A and B disease were evaluated together or hormonal therapy was administered injudiciously [50–55]. Also, in most series, no attempt was made to separate stage A_1 and A_2. Thus, it is impossible to definitively interpret much of the reported literature. Elder et al. recently reported on a series of 25 men with stage A_2 disease treated by radical prostatectomy alone. The follow-up in this series ranged between 9 months to more than 10 years, and 16 patients were followed longer than 4 years. The preliminary results are favorable, since only one patient has developed recurrence of disease, one patient has died without evidence of disease, and 23 patients are alive without evidence of disease. It is likely that radical prostatectomy will offer a long-term cure in these patients, since the tumor was pathologically confined to the prostate in 88% of the surgical specimens. Although the limited follow-up allows for only preliminary conclusions, there does appear to be a therapeutic value for radical prostatectomy in stage A_2 disease, since 33%of similarly staged cases followed at The Johns Hopkins Hospital without treatment developed disease progression within 4 years.

Radical prostatectomy: Stage B_1 disease

Stage B prostatic cancer is subdivided into stage B_1, in which the tumor occupies less than one lobe of prostate (including the discreet palpable nodule

Table 2. Pathologic findings in radical prostatectomy specimens in stage A_2, B_1, B_2 disease stage

		A_2			B_1			B_2		
		No.	Seminal vesicle invasion	Capsule penetration	No.	Seminal vesicle invasion	Capsular penetration	No.	Seminal vesicle invasion	Capsular penetration
Oesterling et al. [73]	1987[a]	23	5	9	175	12	52	58	20	39
Catalona and Dresner [93]	1985[a]	13	1	3	20	0	3	44	14	24
Pontes et al. [94]	1985[a]	5	1	1	9	0	2	40	12	37
Elder et al. [56]	1985[a]	25	2	3						
Fowler and Mills. [95]	1985[a]	16	1	3	48	7	20	11	6	11
Parfitt et al. [96]	1983[a]	26	1	5						
Lange and Narayan [97]	1983[a]	6	3	3	21	5	9	22	9	14
Elder et al. [61]	1982							52	27	32
Bass and Barrett [98]	1980	11	0	0						
Nichols et al. [99]	1977[a]	33	2	0						
Jewett [57]	1970				103	17	11			
Total		160	16 (10%)	27 (17%)	376	41 (11%)	97 (26%)	227	88 (39%)	157 (69%)

[a] indicates that all patients underwent staging pelvic lymphadenectomy.
[b] indicates that some patients underwent staging pelvic lymphadenectomy.

of cancer), and stage B_2, in which the tumor occupies one lobe or more but is still clinically localized to the prostate. The segregation of stage B patients into these biologicaly meaningful subclasses was proposed by Jewett based on a retrospective analysis of 182 patients with clinical stage B cancer who underwent radical perineal prostatectomy at The Johns Hopkins Hospital before January 10, 1951 [57–59].

Pathologic findings in radical prostatectomy specimens indicate that clinical stage B_1 disease is associated with seminal vesicle invasion and capsular penetration in 11% and 26% of cases, respectively (Table 2). Jewett observed that the pathologic finding of capsular penetration in the absence of seminal vesicle invasion did not adversely affect 15-year disease-free survival rates [57]. Seminal vesicle invasion was rarely associated with a 15-year disease-free survival in Jewett's experience [57, 60, 61]. Jewett observed that only 7 of 57 men with clinical stage B_1 disease followed for a minimum of 15 years developed disease recurrence [62]. The staging criteria used by Jewett was limited to plain film radiograms of the bones and the occasional determination of serum acid phosphatase levels. The routine use of staging pelvic lymphadenectomies, radionuclide bone scans, and the determination of serum acid phosphatase and prostate-specific antigen (PSA) levels for staging carcinoma of the prostate should enhance our ability to recognize those men with disease palpably confined to the prostate who have occult metastases.

The survival rate for men with clinical stage B_1 disease undergoing radical prostatectomy has recently been ascertained using cause-specific survival analysis [63]. The primary advantage of cause-specific analysis is that the impact of a specific therapeutic modality on survival is ascertained, since death from a specific disease entity is evaluated. The cause-specific survival curve for men with clinical stage B_1 disease plateaued at 10 years, indicating that the majority of men surviving 10 years following radical prostatectomy are cured of their disease (Fig. 1). The cause-specific survival analysis indicates that men with clinical stage B_1 prostate cancer who undergo radical prostatectomy may be informed that the chance of death from prostate cancer within 15 years of surgery averages $14 \pm 5\%$.

The natural history of stage B_1 disease is unknown, since there is no large cohort of patients who have been followed for long intervals without treatment. Although long-term tumor-free survival has been demonstrated following radical prostatectomy for the treatment of localized prostatic cancer, some have attributed the results to the favorable natural history of prostatic cancer rather than to the therapeutic effect of surgery. In an effort to evaluate this possibility, the Veteran's Administration Cooperative Urological Research Group (VACURG) undertook a randomized multicenter study comparing placebo and radical prostatectomy in patients with clinical stage A and B disease [64–65]. Based on median follow-up intervals of 6.8 and 7.7 years for stages A and B, respectively, they concluded that survival and disease progression were similar in patients treated with either

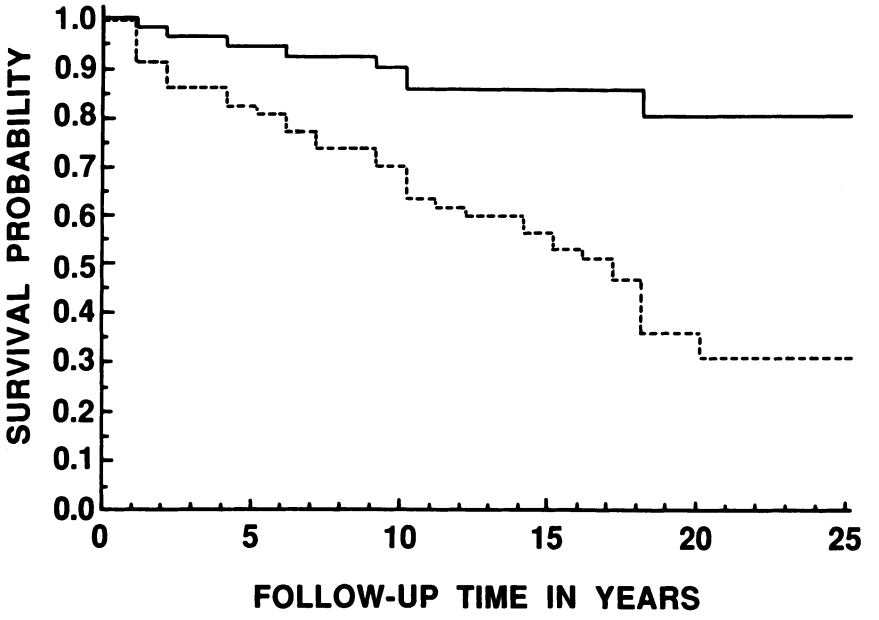

Figure 1. The actuarial survival rates for 57 men with stage B_1 adenocarcinoma of the prostate undergoing radical prostatectomy at the Johns Hopkins Hospital between the years 1951 and 1963. The actuarial survival curves were determined using all cause (----) and cause-specific (——) actuarial survival analysis. A total of 47, 40, and 32 men were alive at 5 years, 10 years, and 15 years, respectively, following radical prostatectomy.

radical prostatectomy or placebo. This study has been criticized because of excessive protocol violations in the placebo group, the absence of staging pelvic lymphadenectomies and bone scans, the fact that 40% of the stage A patients were A_1 patients, the short follow-up interval, and the failure to include progression of the primary lesion in the analysis of progression rates [66]. Although treatment was stated to have been randomly assigned, six of the six poorly differentiated lesions (Gleason grade VIII–X) in the Stage B group were assigned to radical surgery. Indeed, the majority of disease progression in the prostatectomy group occurred in these poorly differentiated tumors. Byar's interpretation of the VACURG study was that the majority of treatment failures resulted from metastases that occurred prior to randomization [67]. This study is only of historic interest since today patients would not undergo radical prostatectomy without obtaining a bone scan or performing a staging pelvic lymphadenectomy. In view of the abovementioned deiciencies of protocol design, it is unlikely that this VACURG study will ever provide meaningful insight into the natural history or the impact of radical prostectomy on localized prostatic carcinoma.

Although a properly designed randomized study has not, and presumably

never will be, performed comparing radical prostatectomy and no treatment for localized prostate cancer, there is a consensus that radical prostatectomy favorably alters the natural course of localized prostate cancer. Radical prostatectomy has been advocated for healthy men with clinically localized carcinoma of the prostate who are less than 70 years of age [68]. Several authors have recently reported the surgical experience for radical cystoprostatectomy in men with invasive bladder cancer over the age of 70 years [69–70]. The operative morbidity and mortality in patients greater than 70 years of age was not significantly different than observed in patients less than 70 years of age. Invasive bladder cancer is usually a very aggressive lesion, and therefore conservative therapy is rarely advised for any individual with a potentially curable lesion. Prostate cancer clinically localized to the prostate also has a tendency to be very aggressive. Chopp and Whitmore have reported preliminary survival data for a group of men with stage B carcinoma of the prostate managed conservatively for a mean interval of 80 months [71]. Disease progression in this series was observed in 15 (33%) of 45 men. This series of conservatively managed patients indicates that stage B disease cannot be assumed to represent a slow-growing process. Middleton has recently summarized survival data for men in the United States between the ages of 70 and 80 [72]. The average life expectancy for men between 70 to 80 years of age ranges between 11.2% and 8.6% years, respectively. The life expectancy data [72], couplied with the disease progression rates [71], indicate that men with stage B prostate cancer greater than 70 years of age will not necessarily succumb to causes of death other than prostate cancer. Middleton has performed radical prostatectomy on 65 men greater than 70 years of age [72]. The morbidity and mortality following radical prostatectomy for men greater than 70 years of age were not significantly different than observed for men less than 70 years of age. The decision to offer radical prostetectomy for healthy men greater than 70 years of age is not unreasonable and should reflect the experience of the surgeon, the general health of the patient, and the preference of the patient.

Radical prostatectomy: Stage B_2 disease

Clinical stage B_2 disease is defined as prostate cancer occupying one lobe or more of the prostate, and palpably confined to the prostate. The criteria for clinical stage B_2 disease presently includes a negative radionuclide bone scan and a normal serum acid phosphatase level. Pathological findings in radical prostatectomy specimens indicate that clinical Stage B_2 disease is associated with seminal vesicle invasion and capsular invasion in 39% and 70% of cases, respectively (Table 2).

Elder and associates observed that 66% of men at Johns Hopkins Hospital with clinical stage B_2 disease undergoing radical prostatectomy between the years 1951–1963 had pathologic evidence of seminal vesicle extension [61].

Between 1981 and 1984, 58 men with clinical stage B_2 prostate cancer underwent radical prostatectomy at Johns Hopkins Hospital [73]. The staging criteria in this group of patients included staging pelvic lymphadenectomies, serum acid phosphatase determinations, and radionuclide bone scans. Thirty-four percent of the prostatectomy specimens had pathologic evidence of seminal vesicle extension. If the presence of seminal vesicle extension implies the presence of occult metastases, a significant proportion of men with clinical stage B_2 disease are unlikely to achieve cure following radical prostatectomy.

Despite improvements in staging criteria, radical prostatectomy is not an optimal treatment for all men with clinical stage B_2 disease. The clinical dilemma is whether to withhold a potentially curative treatment for 66% of the patients with organ-confined disease or to offer a potentially noncurative treatment for 34% of those with seminal vesicle involvement and presumed micrometastasis. The local disease control achieved following radical prostatectomy may justify the surgical intervention for those men not cured of their disease. Hopefully, future improvements in imaging modalities, such as transrectal ultrasound or magnetic resonance imaging, in conjunction with new approaches to pathologic evaluation of biopsy specimens, will aid in the identification of the ideal candidate for surgical cure.

Radical prostatectomy: Stage C disease

Clinical stage C disease represents prostate cancer that on digital rectal examination extends beyond the prostate capsule or into the seminal vesicle. The criteria for clinical stage C disease also includes a negative bone scan and a normal level of serum acid phosphatase. Approximately 60% of men with clinical stage C disease have evidence of lymph node metatases [74, 75]. The majority of men with stage C disease will have microscopic or macroscopic evidence of seminal vesicle invasion [76]. The VACURG study demonstrated that approximately 50% of men with stage C disease will develop evidence of systemic metastases within 5 years [77]. The high incidence of lymph node and seminal vesicle involvement and the poor prognosis associated with lymph node and seminal vesicle involement indicates that radical prostatectomy will seldom cure stage C disease.

Several authors have advocated radical surgery for the treatment of stage C carcinoma of the prostate [76, 78–80]. However, in these series, hormonal therapy was often administered [76, 79, 80]. There is no compelling evidence that the survival of these patients was better than could have been obtained with hormonal therapy alone. In addition, some authors have included clinical stage B patients whose radical prostatectomy specimens demonstrated stage C disease in their survival analysis of stage C patients [76, 79, 80]. This is misleading.

Tomlinson et al. suggested that radical prostatectomy improves the quality of life for men with stage C disease by reducing complications such as urethral

obstruction or ureteral invasion [78]. However, it is unclear whether the two groups of patients in their study (surgical and nonsurgical) were exactly comparable. The realistic therapeutic objectives for stage C disease are local disease control and prolongation of survival. Local disease control may be evaluated according to the control of microscopic disease, palpable disease, or symptoms of bladder outlet obstruction. Since it is generally assumed that stage C is not amenable to cure, the control of symptomatic bladder outlet obstruction is clinically pertinent. There have been no properly designed clinical trials comparing the prevention or improvement of bladder outlet obstruction following TURP, hormonal therapy, radical prostatectomy, and radiotherapy for men with stage C disease. There is also no evidence indicating that survival is enhanced for men with stage C disease following any of the abovementioned treatment options. Paulsen et al. have reported a randomized clinical trial comparing radiation therapy and delayed hormonal therapy for stage C disease [81]. Radiation therapy provided no survival advantage. The therapeutic objective for stage C disease will remain palliative until effective systemic chemotherapy is achieved.

Radical prostatectomy: Stage D_0 disease

Stage D_0 disease is defined as prostate cancer associated with a persistently elevated serum level of acid phosphatase and the absence of bony metastases. Although the positive predictive value of an elevated serum acid phosphatatse in the general male population for carcinoma of the prostate is only 1 in 244 [82], an elevated serum acid phosphatase level in the presence of documented prostate cancer is considered a poor prognostic factor. Whitesel et al. reported that systemic metastases developed in 79% of men with stage D_0 disease followed for 2 years [83]. Based on this clinical series, the recommendation has been made to follow men with stage D_0 disease conservatively and to administer hormonal therapy when metastases become clinically evident. The validity of these recommendations have been criticized since definitive treatment such as radical prostatectomy or radiation therapy was not performed. It is conceivable that systemic metastases may not have developed had definitive treatment been instituted. However, there is no evidence in the literature indicating that men with stage D_0 are cured following radical prostatectomy. Clinical studies comparing survival and local disease control following radical prostatectomy versus delayed hormonal therapy for stage D_0 disease would clarify the role of radical prostatectomy for stage D_0 disease. Until then, radical prostatectomy should be offered to men with stage D_0 disease with the realization that the achievement of cure is unlikely.

Prostate-specific antigen is a more sensitive tumor marker than serum acid phosphatase for prostate cancer [84]. The significance of an elevated prostate-specific antigen level in men with clinically localized carcinoma of

the prostate is unknown. Oesterling et al. have recently correlated PSA levels and pathologic findings in 178 men with clinically localized carcinoma of the prostate undergoing radical prostatectomy [85]. Approximately 10% of men with organ-confined tumors had preoperative PSA levels greater than 10 mg/ml. It is unclear whether those men with elevated PSA levels, clinically localized carcinoma of the prostate, and no pathological evidence extracapsular and seminal vesicle invasion are cured following radical prostatectomy. The prognostic value of PSA will not be realized until the series of Walsh and others are followed for greater intervals of time.

Radical prostatectomy: Stage D_1 disease

It is unlikely that radical surgery will cure any patient with stage D_1 carcinoma of the prostate. This conclusion is based on several lines of reasoning. First, there is no good evidence that prostatic carcinoma metastasizes preferentially to lymphatics. This conclusion is based on the fact that most patients with lymph node metastases developed signs of bone metastases within a short interval thereafter [86–88]. Secondly, it is unlikely that a true therapeutic lymphadenectomy can be performed in the pelvis without removing the rectum because of the wide distribution of lymph nodes in multiple sites in the pelvis in men with carcinoma of the prostate [89]. Third, there is no evidence that radical prostatectomy has influenced long-term survival in patients with stage D_1 disease [90]. In the study by the Uro-Oncology Research Group, the mean time to treatment failure in men with stage D_1 disease after radical surgical, radiation therapy, and delayed hormonal therapy was 18.3 months, 15.8 months, and 22.5 months, respectively [86]. Although surgical cure is unlikely in the presence of metastatic nodal disease, a subgroup of patients may benefit from the local disease control provided by radical prostatectomy. Stage D_1 disease includes a broad spectrum of clinical, histologic, and pathologic disease. Clinical reviews seldom stratify progression and survival according to clinical stage, grade, acid phosphatase levels, and extent of nodal involvement. These are important considerations since it is unlikely that the clinical disease-free interval and survival of the patient with a localized well-differentiated nodule and a solitary metastatic focus in a pelvic lymph node is comparable to an extensively invasive and poorly differentiated lesion with grossly palpable nodal disease. Barzell et al. reported that the probability of being free of subsequent metastases at 5 years after pelvic lymphadenectomy and interstitial implantation of iodine seeds was the same in patients with negative nodes as in patients with positive nodes that were less than a volume of 3 ml [88]. However, with further follow-up of these patients, even those patients with minimal pelvic lymph node metastases demonstrated subsequent progression [91]. More recently, Smith and Middleton showed that the 5-year disease-free progression rate for patients with gross nodal disease was only 15% compared to 27% of those with

microscopic involvement of more than one node and to 44% with a single positive node [92]. Recognizing that patients with low-volume lymph node metastases may have significant 5–10 year progression-free intervals during which time they may experience morbidity from their primary lesion, it may be reasonable to consider radical prostatectomy in selected patients if the surgery can be performed with low morbidity. Specifically, men with clinically localized carcinoma of the prostate and microscopic evidence of lymph node metastases who have a reasonable life expectancy may benefit from the local disease control presumably achieved following radical prostatectomy. Validity for this potential role of radical prostatectomy requires further investigation.

Conclusions

Men with stage A and B_1 carcinoma of the prostate are the optimal candidates for radical prostatectomy since the vast majority of these men have organ-confined disease and will be cured surgically. The majority of men with clinical stage B_2 disease have disease pathologically confined to the prostate. Therefore, radical prostatectomy is offered to these men with a reasonable expectation for achieving cure.

It is generally agreed that men with stage C, D_0, and D_1 carcinoma of the prostate are not candidates for surgical cure, owing to occult systemic metastases. Advocates of radical prostatectomy for stage C, D_0, and D_1 disease have suggested that radical prostatectomy may provide good local disease control and prolongation of disease-free progression. There is no compelling evidence indicating that radical prostatectomy is superior to alternative therapeutic options such as TURP and hormonal therapy for local disease control. The optimal treatment for stage C, D_0, and D_1 disease depends upon the relative morbidity of treatment and the improvement in quality of life provided by treatment. Future clinical protocols should focus on the issues of relative morbidity and efficacy of therapeutic alternatives. The development of effective chemotherapeutic regimens for carcinoma of the prostate will make this controversy of academic interest.

Radical prostatectomy and radiotherapy are the recognized therapeutic options for achieving cure. The optimal treatment for clinically localized prostate cancer is controversial. Radical prostatectomy consistently achieves cure for those lesions that are truly confined to the prostate. There is now sufficient evidence demonstrating that a positive biopsy greater than 12 months after completion of radiation therapy indicates that the treatment has failed to irradicate the local tumor burden [28]. Feriha and Bagshaw reported that the incidence of positive biopsies following external-beam radiotherapy in stage B disease was 50% [29]. In patients with carcinoma localized to the prostate, it seems reasonable to select a form of treatment that can reliably eradicate all of the tumor rather than relying on a form of treatment that

may fail to sterilize the local lesion. Radical prostatectomy represents the preferred therpeutic option for organ-confined disease, owing to the ability of radical prostatectomy to 'cure' prostate cancer confined to the prostate and the ability to perform radical prostatectomy with preservation of urinary continence and erectile function.

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3. Modified retroperitoneal lymphadenectomy for patients with clinical stage I testicular cancer

JEROME P. RICHIE

Carcinoma of the testis is a relatively rare cancer, accounting for only 2% of all cancers in the male. The annual incidence in the United States is 2.5/100,000 males/year [1]. Nonetheless, testicular tumors are the most common malignancy in boys and men between the ages of 15 and 34 years and, until recently, represented the third leading cause of mortality in that age group [2]. The disease, occurring in a crucial evolutionary period of a young man's life, carries a profound social, economic, and emotional impact far beyond its seeming rarity.

Evidence is accumulating that the incidence of testicular cancer is increasing throughout the world. Skinner has reported a two- to threefold increase in incidence in testicular cancer in the Los Angeles County area, and the Dateca Series from Denmark showed a 1.5 times increase in incidence over a 10-year period. This seems to represent a longstanding trend of increased incidence in young white males in Europe and North America [3, 4].

Testicular tumors have been noted at every age period of life, from newborn to the ninth decade. However, there are three peak age groups in which testicular tumors are more common. In the newborn and neonatal period, embryonal-cell carcinoma and yolk-sac tumor represent the most common types of testicular tumor. In the young adult, from 15–34 years, all varieties of germinal-cell tumors occur. In the older age group, above 50, seminomas may occur, but the most common tumor of the testis in that age group is lymphoma.

Major advances in the therapy of testicular cancer have occurred in the past two decades. The prospect for cure and long-term disease-free survival for patients with nonseminomatous germ-cell testicular cancer has improved so greatly that testicular cancer has become one of the most curable solid tumors in the 1980s. Dramatic improvements relate to improved methods of staging and follow-up, improved surgical techniques, and the development of effective platinum-based combination chemotherapy. In the 1980s, long-term disease-free survival rates approach 100% for patients with stage A testicular cancer (limited to the testicle), 95–98% for patients with stage B_1 (less than

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six positive nodes) and approximately the same for patients with stage B_2 disease in the retroperitoneum. Even for patients with bulky retroperitoneal (stage B_3) or pulmonary or visceral metastases (stage C), survival rates have ranged between 60% and 85%.

Cryptorchidism has the strongest etiologic relationship, with a 25- to 50-fold increase in the incidence of malignant degeneration in a patient with cryptorchidism. The incidence of testicular cancer seems to be increased in a patient with an abdominal cryptorchid testis as opposed to an inguinal cryptorchid testis [5]. The likelihood of malignant degeneration seems to be the same whether or not orchiopexy is performed [6]. In patients with a history of cryptorchidism, not only the undescended testis but also the normally descended contralateral testis is at increased risk as well. In approximately one quarter of patients with cryptorchidism who subsequently develop a testicular cancer, the tumor occurs in the normally descended contralateral testis [7]. Thus, there may be some relationship of dysgenesis as an etiologic factor in testicular tumors.

Diagnostic techniques

Clinical

The most common symptoms related to testicular cancer are painless testicular enlargement or mass. Bosl and associates reported pain as an associated finding in 45% of their cases [8]. More commonly, however, the lack of pain, as well as the patient's fear of the diagnosis, result in significant delay in diagnosis from the time of initial recognition of the lesion until orchiectomy. This delay may be as long as 3–6 months in some instances. The length of delay correlates directly with an increased incidence of metastases [9].

The most common symptom attributable to testicular cancer is painless testicular enlargement or a sensation of heaviness in the hemiscrotum. A mass or swelling is the presenting sign in from 70–90% of individuals with testicular cancer. The testicular enlargement is usually gradual, although approximately 10% of individuals report rapid testicular involvement. Trauma may serve to call the individual's attention to the mass. Alternatively, the patient's sexual partner may identify the mass.

In approximately 10% of patients, symptoms referrable to metastases are the initial presenting symptom. These symptoms can include abdominal pain, anorexia, or back pain related to large retroperitoneal metastases. Retroperitoneal lymphadenopathy occasionally results in back pain, although testicular cancers rarely involve the bony skeleton. Patients with advanced pulmonary metastases may present with cough, hemoptysis, or dyspnea on exertion.

Gynecomastia may be seen as one of the early signs of a testicular tumor.

Germ-cell tumors of the testis that produce human chorionic gonadotropin may stimulate the Leydig cells to produce estradiol [10].

Epididymitis or epididymo-orchitis remain the most common misdiagnoses in patients with testicular cancer. Associated inflammation, hemorrhage, or trauma may make initial examination difficult and discrimination of intratesticular from extratesticular masses impossible. Approximately 20% of patients with testicular tumor are initially felt to have epididymitis. If the patient is seen early, the enlarged epididymis can clearly be separated from the testis as a distinct entity. After several days of inflammation, however, differentiation may be impossible. In the past, if clinical circumstances have suggested epididymitis, the recommendation has been antibiotic therapy for several weeks with reevaluation. Testicular ultrasonography can be quite helpful in differentiating intratesticular masses from extratesticular tumors or other lesions that may mimic testicular cancer.

Although the majority of intratesticular masses are malignant, benign intratesticular tumors do exist but are extremely uncommon. The most common benign mass within the testicle is an epidermoid cyst. Usually, this represents a very small nodule just beneath the surface of the tunica albuginea, often with a history of several years' duration. Shah and associates reported a discrete mass, with a mean diameter of 2 cm, in three quarters of the individuals studied [11]. Epidermoid cysts may be difficult to differentiate histologically from teratoma, especially on frozen section. Epidermoid cysts contain keratin but lack other elements. The preferable approach for such a lesion is by inguinal approach, with orchiectomy preferred to excisional biopsy [12].

Testicular ultrasonography

Testicular ultrasonography has become an important diagnostic procedure and essentially an extension of the physical examination. The development of more sophisticated equipment, including 8 and 10 megaherz (MHz) transducers, has increased the specificity and sensitivity of scrotal ultrasonography. The higher megaherz transducers do not require a water bath. The use of high-resolution, real-time scanning has improved imaging considerably. Scrotal ultrasound can now reliably distinguish extratesticular involvement, such as epididymitis, from intratesticular lesions such as tumor. Sample and coworkers reported on 55 patients with a diagnostic accuracy of more than 80% [13]. In 1982, Richie and associates reported on 243 ultrasound examinations, disclosing a high degree of accuracy [14]. Of 22 patients diagnosed by ultrasound to have a tumor, 19 were confirmed and there were three false-negative examinations. There were no false-positive examinations, confirming the importance of ultrasonography as a diagnostic adjunct. Recent studies show a sensitivity and specificity of 100% and 95%, respectively, with 5 and 8 MHz real-time scanners [15].

If a high clinical suspicion exists for the possibility of testicular tumor,

inguinal exploration of the testis is mandatory. Scrotal incisions are absolutely contraindicated, as this alters the lymphatic drainage and, hence, subsequent therapeutic approaches. After division of the external oblique fascia, the spermatic cord is secured at the deep inguinal ring with a Penrose drain to prevent lymphatic spread and the testicle is mobilized into the inguinal incision. Careful palpation of the mass throuh the tunica vaginalis can be performed, and radical orchiectomy can be completed if suspicion of tumor exists. Rarely, a wedge biopsy may be necessary prior to radical orchiectomy.

Staging

Clinical staging serves to predict the presence or absence of residual tumor following orchiectomy as well as the site and extent of the remaining tumor. There are a variety of commonly applied staging systems, with varying degrees of complexity. Basically, however, all staging systems recognize three well-defined stages of tumor spread, as initially advocated by Boden and Gibb [16]: tumor confined to the testis, tumor metastases to the retroperitoneal lymphatics only, or tumor metastases to sites beyond the retroperitoneal lymphatics. Clinical staging is critically important because decisions for treatment are based upon a presumed orderly fashion of metastases, first to the retroperitoneal lymphatics and thence beyond. Furthermore, the extent and volume of metastases have important implications for treatment and prognosis. Therefore, most contemporary staging systems include subcategories to define the parameter of volume of metastases as well as extent.

The two most commonly utilized systems of staging, proposed by Maier [17] and Skinner [18], are outlined in Table 1. A subclassification for patients

Table 1. Staging of testis tumors

Walter Reed General Hospital [22]		Skinner [41]	
IA:	Confined to testis; no clinical or x-ray evidence of spread	A:	Same, but includes no positive nodes on lymph node dissection
IB:	Same as IA, but at lymph node dissection, metastases to iliac or paraaortic lymph nodes	B:	Disease below diaphragm, normal CXR, and mediastinum
II:	Disease below diaphragm/no spread to visceral organs; clinical or x-ray evidence of metastases to para-aortic, femoral, inguinal, and iliac lymph nodes	B_1:	6 positive nodes that are well encapsulated and no extension to retroperitoneal fat
		B_2:	6 positive nodes that are capsulated and retroperitoneal fat extension
II+:	Palpable abdominal mass (> 5 cm)	B_3:	Bulky abdominal mass (> 5 cm)
III:	Disease above diaphragm or spread to body organs (clinical x-ray)	C.	Metastases above diaphragm

Table 2. Extent of disease

IIIA:	Disease confined to supraclavicular lymph nodes.
IIIB-1:	Gynecomastia with or without elevation in biological markers (AFR, HCG).
IIIB-2:	Minimal pulmonary disease (< 5 lesions in each lung field, with none > 2 cm in diameter)
IIIB-3:	Advanced pulmonary disease (any mediastinal, hilar lesion, positive pleural effusion, or pulmonary mass > 2 cm)
IIIB-4:	Advanced abdominal disease (palpable abdominal mass, ureteral displacement, or obstructive uropathy)
IIIB-5:	Visceral disease (excluding lung); liver gatrointestinal tract, central nervous system, inferior vena cava, or bone involvement fall into this category.

with advanced disease is detailed in Table 2. Accurate staging allows for proper selection of the appropriate form of therapy.

A disadvantage of the two-staging systems is a lack of information on the local extent of the primary tumor. A TNM classification proposed by the American College of Surgeons does include a detailed T stage for the evaluation College of Surgeons does include a detailed T stage for the evaluation of the primary tumor [19]. This classification, however, is rather cumbersome and has not met with widespread acceptance.

Clinical evaluation for metastases

After radical orchiectomy and histologic delineation of the neoplasms, staging procedures are used to identify potential sites of metastases. The extent of the staging procedure is dependent upon plans for therapy. With the development of newer technologies, a surfeit of diagnostic tests are available to attempt to delineate retroperitoneal or systemic involvement. With improved technology to detect small metastases, as well as improved chemotherapy to treat the patients with established metastases, controversy exists as to the appropriate diagnostic steps in the evaluation of patients with germ-cell cancers. Should all available tests be used in each patient, regardless of expense? Treatment philosophy becomes an important variable as to whether retroperitoneal node dissection is to be avoided or whether chemotherapy is to be avoided. The recent development of sophisticated radiological techniques, including ultrasound, CT scanning, nuclear medicine imaging, and magnetic resonance imaging, allow focus of different techniques to delineate retroperitoneal or systemic involvement.

Chest x-ray

The pulmonary parenchyma is involved as a site of metastases more commonly than any other location, with the exception of the retroperitoneal lymph glands. A routine chest x-ray will often detect mediastinal or pul-

monary metastases; routine postero-anterior and lateral chest films will detect 85–90% of patients with pulmonary metastases [20]. However, a small number of falsely positive or falsely negative chest x-ray examinations may occur, especially with smaller nodules. Demonstration of pulmonary tumor nodules is of critical importance in planning of therapy, as patients so identified have stage C disease and are therefore treated initially with intensive combination chemotherapy. Without evidence of pulmonary metastases, however, most patients would undergo initial introperitoneal lymphadenectomy or possibly be considered for some expectant observation protocols. Twenty to 30% of patients undergoing initial staging will be found to have pulmonary parenchymal or other intrathoracic metastases [21].

Whole-lung tomography and chest CT scans

Routine chest x-ray can detect chest lesions as small as 1 cm in diameter, but whole-lung tomography can detect lesions as small as 5 or 6 mm in diameter, and computed tomography scanning can detect lesions down to 3 mm in diameter [22]. Nonetheless, as the window of detection becomes narrower, an appreciable lack of specificity occurs, giving rise to false-positive readings by the detection of small pulmonary granulomata. These factors have raised legitimate concerns about the use of whole-lung tomography or CT scanning for routine screening in patients with testicular cancer.

Tumor markers

The term *tumor markers* in testicular cancer refers to several substances elaborated by various cells within testicular tumors: human chorionic gonadotropin (HCG and specifically the beta sublevel), alphafetoprotein (AFP), and lactate dehydrogenase (LDH). Radioimmunoassay techniques for measuring HCG and AFP have provided dramatic improvements in monitoring patients with testicular cancer by markedly increasing the sensitivity of these assays [23]. LDH, although nonspecific, has been demonstrated to be of value, especially in delineation of the extent of metastases [24].

Beta human chorionic gonadotropin. Gonadotropins are composed of two polypeptide chains, the alpha and beta subunit. The beta subunit seems to be responsible for a majority of biologic activity of these hormones. The delineation of a specific antibody for the beta subunit of HCG allows for a very sensitive and specific radioimmunoassay, even in the presence of elevation of luteinizing hormone, which crossreacts with the alpha subunit of HCG [25]. The beta subunit of HCG, used in pregnancy tests in females, is not present in significant amounts in normal males and thus represents a very specific marker of tumor activity. The normal serum level of HCG is below 1 ng/ml, and its half-life in serum is approximately 18–24 hours. HCG, shown to be elaborated by syncytiotrophoblastic cells, is elevated in 100% of patients

with choriocarcinoma, 60% of patients with embryonal carcinoma, 25% of patients with yolk-sac tumors, and less than 10% of patients with pure seminoma [26]. The treatment of patients with pure seminoma but elevation of the beta HCG remains controversial.

Alphafetoprotein. Alphafetoprotein is an alpha 1 globulin that represents the dominant serum protein in the fetal serum of many mammalian species. However, beyond the age of 1 year of life, it is present in only trace amounts in the serum. The normal level is less than 20 ng/ml, and the serum half-life is between 5 and 7 days. Alphafetoprotein was originally described as a marker in patients with hepatocellular carcinoma. The alphafetoprotein is elevated in approximately 70% of patients with embryonal carcinoma and 75% of patients with yolk-sac tumor, but has been absent in patients with choriocarcinoma or with pure seminoma [26].

The expense of obtaining the beta subunit of HCG or alphafetoprotein preclude their use as screening for large patient populations. Their major impact has been as an adjunct to histologic staging, especially alphafetoprotein elevation in patients with seminoma, and as a means of following patients both prior to therapy and during therapy to give some indication of response to treatment.

There may be a discordance between tumor markers, so both AFP and HCG must be measured sequentially. There are very few false-negative elevations of tumor markers, so consistently elevated tumor markers following therapy do indicate residual active disease, assuming that the elevation does not represent appropriate reduction by the normal seum half-life. Nonetheless, there are significant limitations to the specificity of negative tumor markers. Return of markers to normal after therapy does not assure that all viable tumor has been removed or obliterated. Skinner and Scardino reported that almost 80% of patients whose markers normalized after chemotherapy were still found to have viable tumor at the time of extirpative surgery [27]. Likewise, Donohue reported on histologic findings of 50 patients who underwent cytoreductive surgery after chemotherapy. In 19, residual cancer was found but only 6 of the 19 had elevated tumor markers at the time of exploration [28].

Although most patients with extensive metastatic disease will have elevation of either the AFP or beta HGC after orchiectomy but prior to implementation of other therapeutic procedures, in patients with less advanced disease, prelymphadenectomy marker elevation does not correlate as well with pathologic findings. Skinner and Scardino reported that 50% of patients with stage B_1 disease had elevated markers after orchiectomy alone, and 64% of patients with stage B_2 disease had elevated markers prior to lymphadenectomy [27]. However, this means that 50% of patients with stage B_1 and 36% of those with stage B_2 had false-negative rates, even with documented metastases in the retroperitoneum. These data have been confirmed by Bosl and associates [29]. Thus, negative tumor markers do not preclude the

presence of disease in the retroperitoneum, and caution should be the watch-word when therapeutic decisions concerning lymphadenectomy are influenced by apparently normal marker values.

CT scan

Germ-cell tumors of the testis spread initially to the retroperitoneal lymph nodes and thence to supradiaphragmatic lymph nodes, lungs, and other sites of systemic involvement. Until recently, determination of abdominal metastases has been based upon physical examination, excretory urography, inferior venacavography, and bipedal lymphangiography. However, all these techniques have a limited ability to delineate accurately the degree of retroperitoneal nodal involvement. Computerized tomography (CT) scan has been suggested as a technique with a high degree of accuracy in the depiction of retroperitoneal lymph node involvement in patients with testicular tumors. Because of the more accurate depiction of the extent of nodal metastases, CT scan has largely replaced the more invasive lymphangiography for depiction of retroperitoneal disease. CT scanning of the retroperitoneum has shown a high, more than 90%, rate of prediction of metastases in patients with lymphoma [30]. Several early series seemed to confirm the capability of the CT scan to correctly predict the extent of retroperitoneal involvement. Lee and associates reported that 9/10 patients with testicular tumor and pathologic confirmation were assessed correctly by the CT scan [31]. Other investigators confirmed the accuracy of the CT scan in depicting retroperitoneal nodal involvement in patients with extensive or moderate amounts of disease in the retroperitoneum. However, the importance of the CT scan should lie not only in its ability to depict retroperitoneal involvement, but also in the confidence gained from a negative scan, i.e., the predictive value of a negative scan, especially when one considers the possibility of observation versus retroperitoneal lymph node dissection.

In 1982, Richie and associates reported on a prospective study of 30 patients with all stages of testis tumor who underwent CT scan within 1 week prior to retroperitoneal lymphadenectomy [32]. The sensitivity was 65% and the specificity was 90%, giving an overall accuracy of 73%. Most importantly, however, of 16 CT scans interpreted as normal, 7 (44%) proved to be falsely negative. Thus, the predictive value of a negative scan in our series was only 56%. This high false-negative rate has been confirmed by several other centers, including Sloan Kettering and Indiana University.

Undoubtedly, improvements in CT scanning techniques invariably will result in improved accuracy and diminished false-negative rates for the depiction of retroperitoneal lymph node involvement in patients with testicular tumors. As newer scanners become available, shorter scanning times and narrower tissue slices will improve pictorial quality and, therefore, interpretation. One of the limitations of CT scanning is the difficulty in separating

intraperitoneal from retroperitoneal contents in thin patients without adequate fat planes for delineation. Repetitive administration of oral contrast agents may help to reduce this problem of interpretation as well.

CT scanning appears to be a highly accurate method for the depiction of bulky or extensive retroperitoneal disease stage II± or III. However, the normal CT examination still does not approach the accuracy level in which retroperitoneal nodal metastases can be excluded with confidence.

Bipedal lymphangiography has been utilized to evaluate retroperitoneal lymph nodes since 1955 [33]. Many centers have utilized lymphangiography as the standard technique for determining regional retroperitoneal lymph node involvement in patients with testicular tumor. Although testicular lymphangiography would probably provide better visualization of the nodes draining the testis, practical considerations have favored the bipedal lymphangiography route instead.

The major concern with lymphangiography has to do with its ability to identify small volume nodal metastases. Excellent reviews on the subject of lymphangiography in patients with testicular cancer are available [34]. Lymphography should include both a filling or lymphatic phase and a nodal phase of the lymphangiogram, with criteria for positive studies being marginal filling defects, lymph vessel deviation, lymphatic blockage, or nonfilling of lymph nodes. In Wobbes' series of lymphography, pathologic examination revealed a false-negative predictive value rate of 16/61 patients [35]. Thus, the accuracy rate and predictive value of a negative test in lymphangiography seem, similar, or certainly no better, than the rates reported with CT scanning. Overall accuracy of lymphangiography has ranged from 62% [36] to a high of 89% [37].

Because lymphangiography is an invasive technique with potential complications such as fever, local pain, superficial would infection, or more serious complications such as pulmonary dysfunction, my preference is to avoid lymphangiography and utilize the CT scan as the primary method of staging of the retroperitoneal lymph nodes.

When lymphography and CT scanning are combined, no significant difference among either group can be appreciated. Ultrasonography likewise does not seem to be more effective in evaluation of retroperitoneal lymph node dissections than is CT scan.

Vugrin et al. [38] from Sloan Kettering Memorial Hospital and Rowland et al. [39] from Indiana University have correlated clinical staging with pathologic findings in patients with stage B_1, B_2, and B_3 retroperitoneal metastases utilizing CT scan, ultrasound, tumor markers, and/or lymphangiography. In both of these series, pathologic stage correlated with the clinical stage in only 36–46% of patients with stage B_1 disease, 67–73% for stage B_2 disease, and 100% for stage B_3 disease. Thus, all staging modalities fall far short of accurately predicting minimal or even moderate retroperitoneal lymph node involvement.

Therapy

Given the impressive and durable survival rates for patients with almost all stages of testicular cancer, attention has been turned to issues of quality of life as therapy becomes fine tuned for each individual. Because testicular cancer is a disease of relatively young men, who are planning families as well as career opportunities, long-term fertility post-treatment has assumed an important role. Prior to the 1980s, prospects for fertility in patients with testicular tumors were limited. The standard retroperitoneal lymph node dissection (RPLND) almost uniformly resulted in ejaculatory dysfunction, either by failure of seminal emission or retrograde ejaculation. Approximately 90% of the patients who underwent RPLND were so afflicted, with resultant infertility but not impotence. Because a substantial number of patients with nonseminomatous germ-cell tumors had evidence of impaired spermatogenesis either before or immediately following radical orchiectomy, it was felt that preservation of ejaculation was not that important. Furthermore, patients who received chemotherapy universally had impaired spermatogenesis, thought to be of a permanent nature.

As knowledge concerning potential treatments of patients with testicular cancer has increased, so too has our understanding of the mechanisms of ejaculatory dysfunction as well as the potential for recovery of spermatogenesis in patients treated for nonseminomatous germ-cell tumors of the testis. These issues, and the impact on modification of therapy, will be considered subsequently.

Fertility

Semen quality as an indicator of potential fertility has been studied by many investigators before, during, and after various treatments for testicular cancer. Approximately 50–60% of males are reportedly subfertile at the time of diagnosis of a nonseminomatous germ-cell tumor. Controversy exists as to whether spermatogenesis is impaired prior to the clinical manifestation of testicular cancer or whether semen quality is impaired as a result of diagnosis and/or initial therapy. Nonetheless, in a large proportion of patients, spermatogenesis impairment may be reversible.

There are several factors that impact upon fertility problems and suggest the possibility of some preexistent condition that may in and of itself contribute to the development of a testicular cancer. The incidence of testicular neoplasm in patients with a cryptorchid testis is 25–50 times more frequent than in patients with normally descended testes. Even though the cryptorchid testis is at higher risk, the contralateral 'normal' testis is also at increased risk to develop malignancy and may be associated with impaired spermatogenesis as well. In patients who have had semen analyses immediately prior to or subsequent to radical orchiectomy, sperm counts are generally low. The associated incidence of carcinoma in situ in patients with

crytorchidism [40] ranges between 3% and 8%. There is also an association of carcinoma in situ in patients who present with infertility.

The above factors would suggest that impaired spermatogenesis may be of etiological import in the development of testicular cancer. Data from large series would suggest that 60–75% of patients with nonseminomatous germ-cell tumors are subfertile at the time of diagnosis [41]. In approximately one third of patients, the infertility may well be irreversible. In the remaining patients, subfertility may be temporary, with potential recovery dependent upon the treatment rendered. Thus, the majority of patients with nonseminomatous germ-cell tumors of the testis should have the potential return of fertility as long as it is not impaired by other treatment modalities. These data have important implications in consideration of sperm-banking prior to definitive therapy. Skinner and associates reported that approximately 60% of males did not have adequate sperm patterns after freeze-thaw analysis to permit sperm-banking [41]. However, approximately 40% will have a reasonable sperm pattern to permit sperm-banking. Even in patients whose sperm counts are marginal, sperm-banking may be beneficial, especially with improving techniques of in-vitro fertilization.

Emission and ejaculation

Up until 1980, virtually every article in the literature reported a high incidence of infertility following retroperitoneal lymph node dissection in patients with testicular cancer. This infertility was largely due to either failure of seminal emission or retrograde ejaculation secondary to damage to the sympathetic nerve fibers involved in ejaculation. In order to understand modifications that have been made in node dissections in an attempt to preserve ejaculation, a brief review of the neuroanatomy of ejaculation is indicated.

Seminal ejaculation depends on emission from the contraction of the ampullary portion of the vas, seminal vesicle, and periurethral glands along with closure of the internal sphincter and bladder neck mechanism. Ejaculation is then caused by expulsion of seminal fluid under sympathetic control via contraction of the bulbourethral and periurethral musculature. Both seminal emission and ejaculation are innervated via the thoracolumbar sympathetic trunk. Sympathetic fibers from T12–L3 emerge from the sympathetic ganglia and converge anterior to the aorta. Fibers from both sides intermingle and pass along the aortic bifurcation anterior to the common iliac arteries, emerging in the true pelvis as the hypogastric plexus. These sympathetic fibers then travel via pelvic nerves to innervate the vas deferens, seminal vesicles, prostate, and bladder neck. Although injury to both sympathetic chains will most likely destroy ejaculation, injury to the areas surrounding the aortic bifurcation bilaterally will almost universally cause ejaculatory dysfunction.

Early descriptions of retroperitoneal lymphadenectomy included a complete bilateral dissection from above the renal hilar area bilaterally, encompassing both ureters down to where each ureter crossed the common iliac artery (Fig. 1) [42]. Retroperitoneal tissue was removed both anterior to and posterior to the great vessels in order to completely remove all nodal-bearing tissue. Thorough removal of all lymphatic tissue was considered essential because of the lack of effective alternative therapies. Indeed, retroperitoneal lymph node dissection using the above template has been curative in patients with minimal nodal involvement, even without the use of adjunctive chemotherapy [43]. With the development of effective combination platinum-based chemotherapy, testicular cancer has become one of the most curable of all genitourinary tumors. As survival rates have improved, the long-term effects of infertility resulting from retroperitoneal lymph node dissection have assumed greater import. A major impetus for close observation or surveillance therapy has been the long-term effect of ejaculatory compromise and infertility in patients with low-stage testicular cancer.

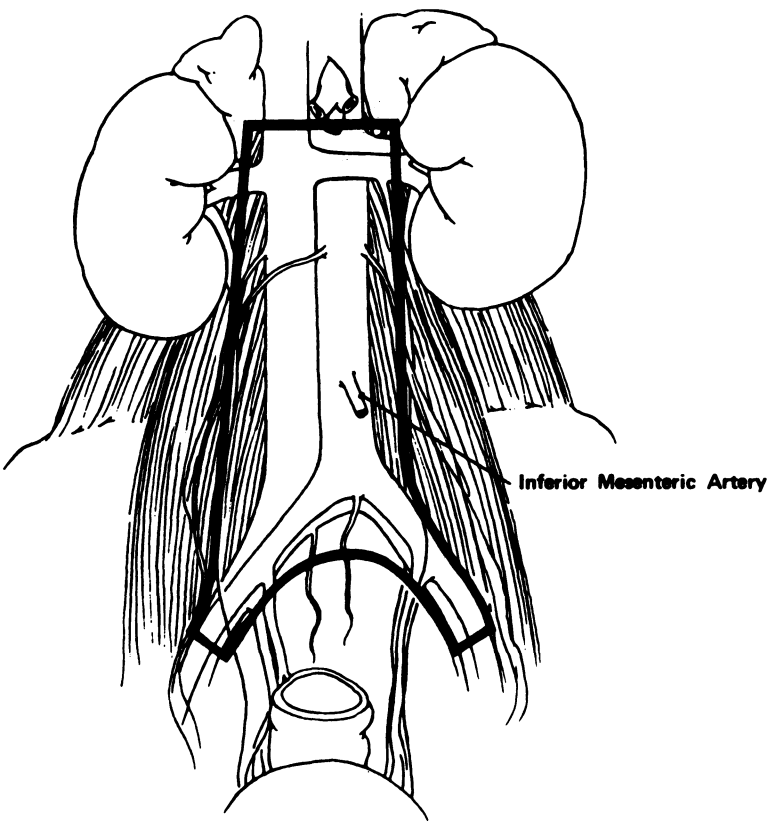

Figure 1. Standard template for left-sided retroperitoneal lymph node dissection. (Reproduced from Whitemore with permission.)

In the early 1980s, Narayan and associates published an important paper concerning ejaculation after extended retroperitoneal lymph node dissection [44]. This paper showed that modification of surgical boundaries could allow return of ejaculation in approximately half of patients with low-stage testicular cancer following retroperitoneal lymph node dissection. Even with more extensive dissections for stage B_2 or B_3 retroperitoneal involvement, ejaculatory capability returned in approximately one third of patients. Based upon the anatomic understanding of the neural pathways for control of emission and ejaculation, coupled with knowledge of primary landing sites in patients with low-stage testicular cancer, we embarked upon a modified retroperitoneal lymph node dissection to preserve these neural pathways and abrogate problems of ejaculatory compromise.

Methods

Beginning in 1982, a modified lymph node dissection has been performed in 52 patients with clinical stage 1 nonseminomatous germ-cell tumor of the testis. The modification is a modified bilateral dissection. The dissection is bilateral above the level of the inferior mesenteric artery, but unilateral below the inferior mesenteric artery, unless there is evidence of visible tumor near the inferior mesenteric artery (Figs. 2 and 3). The technique involves a thoracoabdominal approach through the ipsilateral side, with mobilization of the peritoneal envelope completely as previously described. Once the peritoneum is peeled from the posterior rectus fascia, an incision is made in the peritoneum and palpation carried out to be certain there is no bulk disease or more extensive disease that would preclude retroperitoneal rather than transperitoneal lymphadenectomy. By peeling the peritoneal envelope and remaining in a retroperitoneal fashion, along with preservation of the inferior mesenteric artery, injury to the sympathetic nerves located on the contralateral side of the aorta and great vessels below the inferior mesenteric artery is avoided.

It should be emphasized that the dissection is a full bilateral dissection above the inferior mesenteric artery. All lumbar veins and lumbar arteries from the level of the inferior mesenteric artery to the renal vessels are sacrified in order to remove nodal-bearing tissue posterior to the vena cava and aorta. There is no place for node sampling or node plucking in this procedure. The patients potentially most curable are those with microscopic metastatic involvement, which certainly would be missed by a node-sampling technique. The modification below the inferior mesenteric artery allows complete dissection of the ipsilateral great vessel, including the common iliac artery and the ipsilateral side of the aorta, but precludes dissection on the contralateral side of the great vessel. Thus, for a right-sided tumor (Fig. 2), the dissection would encompass the renal hilar area bilaterally to the level of the left ureter or gonadal vein. On the left side, dissection is carried down

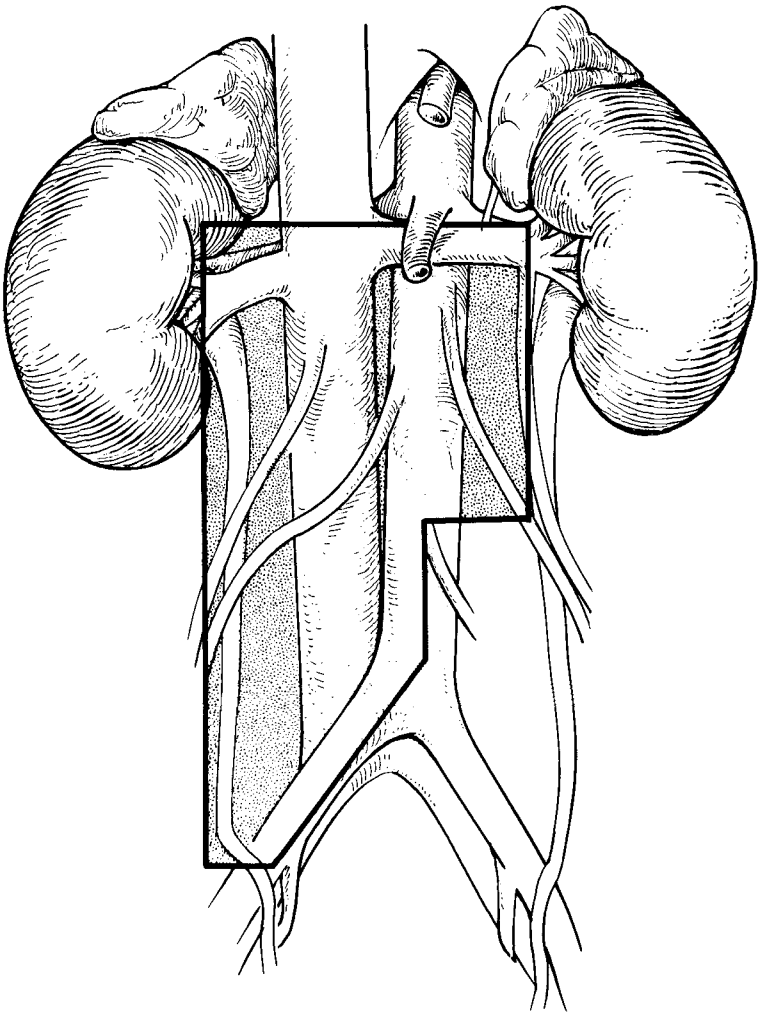

Figure 2. Modified right retroperitoneal lymph node dissection template. Note that this represents a complete bilateral dissection above the level of the inferior mesenteric artery and a unilateral dissection below the inferior mesenteric artery.

to the level of the inferior mesenteric artery, then across to the right side and down the right side of the aorta encompassing the right common iliac artery. All nodal-bearing tissue in the interaortal caval area is removed, and posteriorly the margin is the anterior spinous ligament. Both sympathetic chains are preserved. On the right side, the dissection is carried along the right renal hilar area to the level of the right ureter and down to where the ureter crosses the common iliac artery. The ipsilateral spermatic vessels are removed to the level of the deep inguinal ring and the previously ligated stump of the cord.

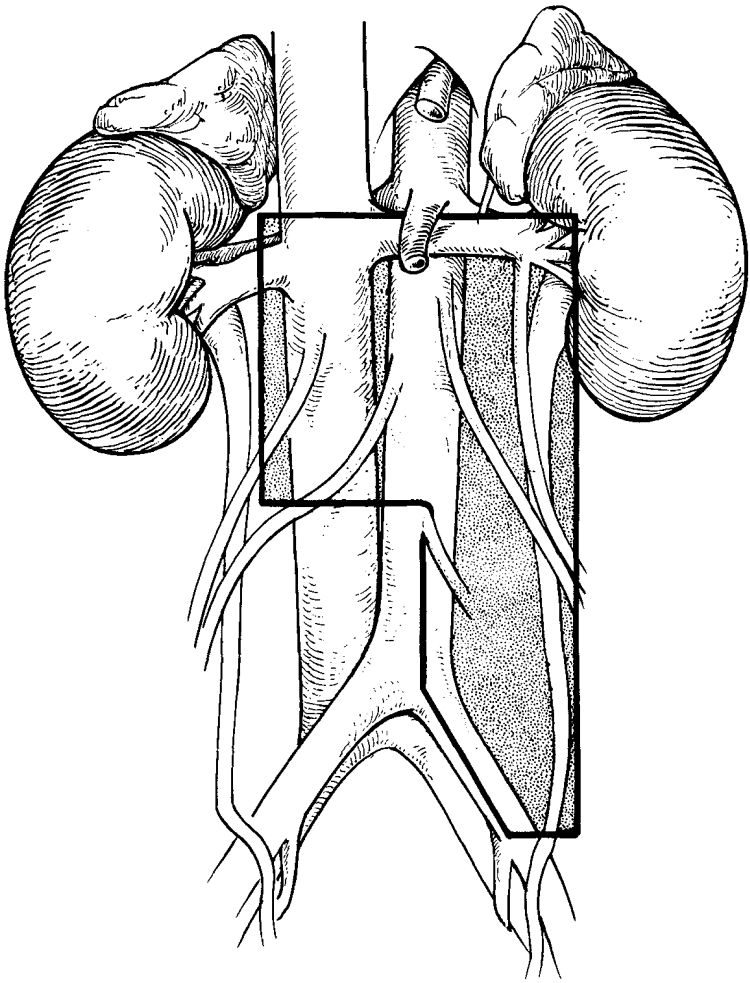

Figure 3. Modified template for a left-sided retroperitoneal lymph node dissection.

For left-sided dissection (Fig. 3), a similar dissection is performed, with the exception of the right lateral margin. Since nodal spread tends to be from right to left, dissection is only carried to the lateral margin of the inferior vena cava rather than all the way over to the right ureter. This dissection is bilateral above the inferior mesenteric artery and unilateral below the inferior mesenteric artery.

It is essential to emphasize that this dissection should be utilized in patients without grossly positive lymph nodes. In patients with more extensive (B_2) disease, blocked lymphatics can result in retrograde flow and more extensive involvement of other areas not likely to be involved in patients with low-stage disease.

From 1982 to 1987, modified retroperitoneal lymph node dissection was

performed in 51 patients, aged 16 to 48 years. In 22 patients the primary tumor was on the left side, and in 30 the primary tumor was on the right side. It should be emphasized that 11 additional patients were explored and required full retroperitoneal lymph node dissection for more extensive involvement than was suspected on the basis of initial staging, including markers, CT scan, etc. Thus, even in the late 1980s, a significant incidence of understaging exists in patients with low-stage disease, a fact that must be kept in mind when surveillance protocols are considered.

The boundaries of the dissection described above can be superimposed over the mapping studies of Donohue and associates [45]. The surgical boundaries described above encompass virtually all nodes that would be involved in patients with low-stage (stage B_1) testicular cancer for right-sided tumors (Fig. 4) as well as left-sided tumors.

A modified dissection is somewhat more difficult to perform than a full retroperitoneal lymph node dissection. This is because preservation of the

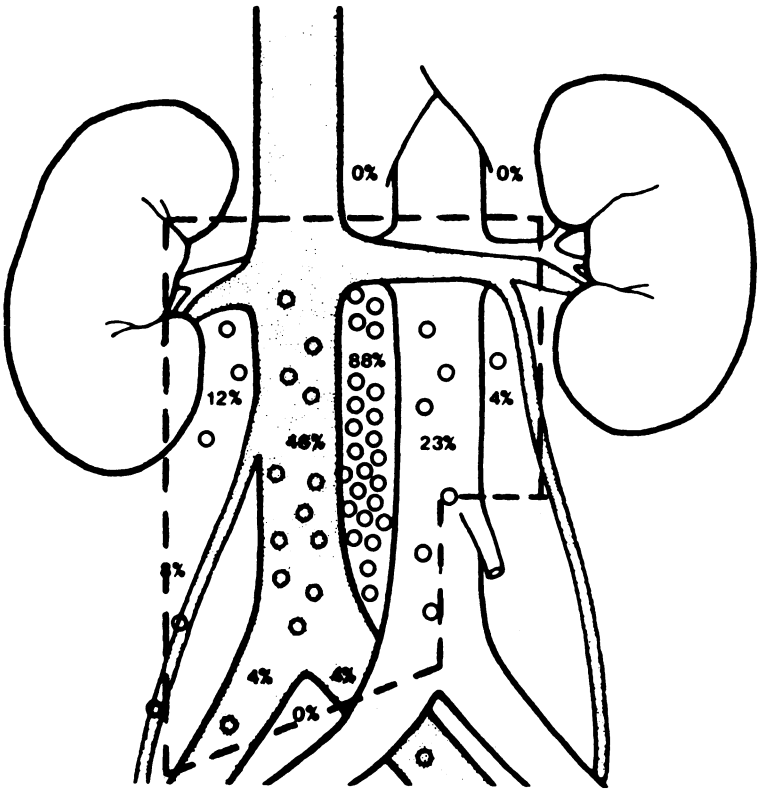

Figure 4. Superimposition of right-sided modified template over the primary landing zone site for patients with minimal stage (stage B_1) nonseminomatous germ-cell tumor involving retroperitoneal lymph nodes. (Reproduced from Donohue and associates with permission.)

lumbar vessels on the contralateral side below the inferior mesenteric artery limits the mobility of the great vessels. Nonetheless, with experience, operative time has averaged 3½ hours and blood loss has been minimal. The chest tube remains for 24 to 48 hours, and a nasogastric tube is used overnight if at all. This represents an added benefit of the retroperitoneal rather than the transabdominal approach. Most patients are discharged on the fifth or sixth day postoperatively.

The final pathology report of the 52 patients who underwent modified retroperitoneal lymph node dissection was stage A in 39 patients and stage B_1in 13 patients. One patient who had stage B_1 disease but involvement in three different areas received postoperative chemotherapy of vinblastine, bleomycin, and cisplatinum.

Patients have been followed from 12 to 64 months with a median of 28 months. Four patients have relapsed, all with pulmonary metastases. All four patients have been salvaged with chemotherapy and remain free of disease. There have been no retroperitoneal recurrences.

With respect to preservation of ejaculatory function, 46 of 52 patients have reported spontaneous return of antegrade ejaculation, usually within 1 month postoperatively. An additional three patients have been converted to antegrade ejaculation with imipramine (Tofranil). Thus, 49 of 52 patients (94%) have recovered antegrade ejaculation, either spontaneously or with medication. Three patients remain with retrograde ejaculation, as documented by sperm in the urine post ejaculation. Sperm counts have been obtained in 32 patients. The counts range from a low of 2×10^6/ml to a high of 113×10^6/ml. Volume has ranged from 0.8 ml to 4.0 ml. Most patients report that postnode dissection ejaculate volume is approximately one half that of prenode dissection ejaculate volume. Thus far, there have been seven pregnancies in this group of patients.

Discussion

The template or boundary method of retroperitoneal lymph node dissection has significant advantages. By utilization of this technique, a complete bilateral dissection can be performed in the area most likely to be involved with retroperitoneal nodal disease, yet modification in a less likely area can spare some of the ejaculatory consequences. This type of procedure is universally transferable to surgeons with some experience in performance of retroperitoneal lymph node dissection and requires no additional new skills or techniques of identification. Certainly, preservation of both ipsilateral and contralateral sympathetic chains can be performed if care is taken. The above techniques represent a therapeutically and diagnostically sound technique for treatment of patients with pathologic stage A and B_1 disease, with preservation of ejaculation in more than 90% of patients.

Various centers have described modifications of retroperitoneal lymph

node dissection with a variety of techniques to preserve ejaculation. Donohue reported modifications with preservation of ejaculation in two thirds of patients with right-sided tumors and in one third of those with left-sided tumors [46]. Pizzocaro reported on unilateral retroperitoneal lymph node dissection with excellent preservation of ejaculation [47]. Ninety percent of patients with stage A and B_1 testicular cancer had preservation of ejaculation, whereas only 23% of patients with stage B_2 had preservation of ejaculation.

Recently, attempts have been made to identify individual retroperitoneal sympathetic nerves responsible for antegrade ejaculation. Jewett and associates describe early experience with nerve-sparing techniques with excellent return of ejaculation [48]. Likewise, Rowland and Donohue have performed a similar procedure with excellent return or ejaculation in short-term follow-up [49].

In patients whose ability to ejaculate after retroperitoneal lymph node dissection does not return, a variety of treatments are available. Alpha-adrenergic agents such as ephedrine have been utilized along with imipramine or Tofranil with varied results. Three of my patients responded to imipramine, 25–50 mg given 1–2 hours prior to ejaculation. Lange and associates have reported good results with psuedoephedrine hydrochloride, 90 mg hourly for 2 hours prior to ejaculation [50]. Ornade in a twice daily dosage has also reportedly been effective. Most recently, transrectal electrical stimulation has been used to treat patients with impaired ejaculation after retroperitoneal lymph node dissection and may well have promise in the future [51].

The success of a variety of nerve-sparing techniques to preserve normal antegrade ejaculation clearly indicates that this is a universally applicable phenomenon in capable hands. Nonetheless, since some patients may be understaged with more extensive disease, sperm-banking is recommended as a routine prior to retroperitoneal lymph node dissection in patients with low-stage disease. Retroperitoneal lymphadenectomy via a modified technique would seem to offer an effective therapeutic alternative to observation protocols. Modified techniques allow complete removal of nodes around the primary landing site and markedly decrease postoperative complications with ejaculation. Furthermore, these techniques reduce the concern about retroperitoneal understaging. Identification of further risk factors in the primary tumor, such as vascular invasion and percent of teratoma, as well as pathologic T stage of the tumor, can help to segregate that subset of patients who will do well with surveillance protocols vis-à-vis a larger subset of patients who would potentially benefit from modified retroperitoneal lymph node dissection [52]. Clearly, if better staging techniques could be delineated to absolutely identify the presence or absence of retroperitoneal lymph nodes, then even modified lymph node dissections would be unnecessary. In 1989, however, our staging techniques are far from perfect and thus a major role remains in the surgical armamentarium for modified retroperitoneal lymph node dissection.

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4. Penile carcinoma: The case for primary lymphadenectomy

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Carcinoma of the penis remains a disease that is curable only when complete surgical excision is possible. Even the most aggressive attempts to control this disease with cytotoxic chemotherapy and radiation have met with dismal results. On the other hand, the surgery necessary to eradicate this disease is both mutilating and morbid. The combination of these factors has led many to take a nonaggressive approach to the management of these patients. Much of the confusion regarding the management of penile carcinoma stems from the lack of a generally accepted clinical staging system. Most reports have employed some modification of the staging system originally published by Jackson in 1966 [1]. This staging system was a retrospective pathological classification that has been extrapolated to the clinical setting. Unfortunately, the correlation between clinical stage and pathological stage has been shown repeatedly to be quite poor in this disease [2]. In addition, the original Jackson staging system did not distinguish between superficial and invasive lesions. Instead, a distinction was made between tumors confined to the glans or prepuce and those extending onto the shaft of the penis. Thus, reports utilizing the Jackson staging system are difficult to extrapolate to patient management decisions. This is particularly the case in deciding who should and who should not undergo lymphadenectomy.

It is generally reported that approximately half of patients with penile carcinoma will have clinically suspicious lymph nodes at presentation, but only half of these will harbor a tumor at the time of inguinal lymphadenectomy. Conversely, the reported incidence of clinically negative but pathologically positive inguinal lymph nodes ranges from 11% to 45% [2–5]. These statistics emphasize the importance of being able to more accurately predict the presence of inguinal metastases prior to lymphadenectomy.

The clinical staging system employed at the Vanderbilt University Affiliated Hospitals is detailed in table 2. This staging system is a combined clinical and pathologic staging system and has been developed in order to aid in selecting patients for lymphadenectomy. The primary lesion is evaluated pathologically for grade and depth of penetration. The clinical staging of the inguinal lymph nodes is deferred for 4–6 weeks following eradication of the primary lesion so that the accompanying infectious process in the lymph

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Table 1. Jackson staging system for penile carcinoma

Stage I:	Tumors confined to the glans and/or prepuce
Stage II:	Tumors extending onto the shaft of the penis
Stage III:	Those with malignant, but operable, groin nodes
Stage IV:	Those with a primary tumor extending off the shaft of the penis and/or those with inoperable groin nodes or distant metastases

Table 2. Vanderbilt staging system for penile carcinoma

Stage I:	Superficial carcinoma; no invasion of corpora cavernosa, corpora spongiosum, or scrotum; normal inguinal lymph nodes
Stage II:	Infiltrating carcinoma with invasion of corpora cavernosa, corpora spongiosum, or scrotum; normal inguinal lymph nodes
Stage III:	Superficial or infiltrating carcinoma with enlarged inguinal lymph nodes
Stage IV:	Unresectable groin nodes and/or distant metastatic disease

nodes can be sterilized with antibiotic therapy. Additionally, a metastatic survey is conducted that generally includes a chest radiograph, liver function studies, and abdominal and pelvic CT scan. The intent of our staging system has been to sort out those candidates for ilioinguinal lymphadenectomy so as to maximize our cure rates while simultaneously minimizing our morbidity. In the following sections, the authors will summarize the available literature according to our staging system as well as present our own results, which have recently been reported [6].

Stage I penile carcinoma

Stage I or noninvasive penile carcinomas rarely metastasize. Most series in the literature do not distinguish between superficial and invasive primary lesions. deKernion et al. reported the Case Western Reserve experience with 48 patients with squamous-cell carcinoma of the penis treated between 1954 and 1969 [2]. There were 13 patients in this group with superficial penile lesions and clinically normal inguinal lymph nodes. None of these patients underwent inguinal lymphadenectomy. Ninety-two percent of these patients (12/13) survived more than three years without evidence of recurrent disease. One patient did succumb to metastatic disease.

Fraley et al. [7] have recently reported the results from the University of Minnesota for the management of carcinoma of the penis [7]. There were 61 patients with Jackson stage I disease. Twelve of these patients died of their tumors, yielding a disease-specific death rate of 20%. This is much higher than our experience with this stage of the disease, and it highlights the incon-

sistency of the Jackson staging system. Close scrutiny of their results offers an explanation for this apparent discrepancy. In this series, no distinction was made between superficial and invasive primary lesions. Of the 17 patients with tumors less than 3 cm in diameter that were confined to the glans or prepuce, only three (18%) died of their carcinoma. Of these three patients, two had been treated by local excision and failed, and the third was noted to have urethral invasion. Thus, of the 14 patients whose primary lesion was eradicated and probably did not have invasive lesions, none died of metastatic disease.

The Vanderbilt experience has been similar to the abovementioned clinical research. We have had the opportunity to manage 19 patients with noninvasive carcinoma and clinically negative inguinal lymph nodes. None of our patients underwent inguinal lymph node dissection. With a minimum follow-up of 5 years, none of these patients developed inguinal metastases and none died of disseminated disease.

From these series it is apparent that metastatic disease in inguinal lymph nodes is extremely unlikely in the patient with an adequately treated, superficial squamous-cell carcinoma of the penis. We strongly believe that 'prophylactic' inguinal lymphadenectomy is not indicated in this group of patients; instead, close follow-up with careful examination for recurrence of the primary or inguinal adenopathy is in order.

Stage II penile carcinoma

The management of patients with stage II penile carcinoma remains highly controversial. A number of studies suggest a high incidence of inguinal lymph node metastases in this stage of the disease.

Skinner et al. [3] presented results on 18 patients with penile carcinoma and clinically negative lymph nodes. The number with superficial and invasive lesions was not specified. Of these patients, three died of metastatic disease without further surgery. Five other patients developed inguinal lymphadenopathy on follow-up and four of these underwent lymphadenectomy. Three of the five patients who developed inguinal lymphadenopathy were salvaged

Table 3. Incidence of lymph node metastases with clinical stage II penile carcinoma

	% pathologically positive nodes or disease progression
Skinner et al. [3]	44%[a]
deKernion et al. [2]	38%
Fraley et al. [7]	36%
McDougal et al. [6]	52%

[a] Includes patients with stage I primary lesions

by lymphadenectomy. Thus, a total of 8 out of 18 patients (44%) without clinically suspicious nodes subsequently developed disease progression.

In the report of deKernion et al. [2], eight patients had invasive penile lesions and clinically negative lymph nodes. None of their patients underwent inguinal lymphadenectomy, and only five patients survived 3 years without disease. While it is not specifically stated, the other three presumably died of disease progression, yielding a 38% disease progression rate.

Fraley et al. [7] summarized their results in patients with UICC [8] clinical stage $T_3N_0M_0$ or $T_4N_0M_0$ penile carcinomas. A clinical stage T_3 lesion is one that is greater than 5 cm and invades the corpora or urethra, while T_4 is invasive to adjacent structures. Two patients died of metastatic disease, one developed groin metastases and succumbed to an unrelated condition, and one had a positive lymph node at the time of inguinal lymphadenectomy. Overall, 36% of patients developed disease progression or had inguinal metastases at lymphadenectomy.

The Vanderbilt experience has again yielded similar results. A total of 23 patients presented with clinical stage II disease, that is, an invasive primary lesion and no palpable evidence of inguinal lymphadenopathy. Nine of these patients underwent early inguinal lymphadenectomy, and six of these had microscopic nodal metastases. Fourteen patients did not undergo early inguinal lymphadenectomy, and only six of these survived free of disease. Thus, a total of 12 out of the 23 patients (52%) either had microscopic nodal metastases at the time of lymphadenectomy or developed disease progression on follow-up. Thus, these four series would suggest a 36% to 52% incidence of inguinal lymph node involvement in patients with invasive penile carcinomas and would argue strongly in favor of early inguinal lymph node dissection in this population of patients.

The opposite viewpoint has been put forward by Beggs and Spratt [9] in 1964 and in a follow-up study from that same institution in 1976 [10]. Beggs and Spratt summarized their results with the management of 88 patients with penile carcinoma treated between 1940 and 1961. Twelve patients underwent early ('prophylactic') inguinal lymph node dissection, and only two (17%) had histologically proven nodal metastases. A total of 50 patients were thought to have clinically normal inguinal lymph nodes at presentation, and 10 of these (20%) developed inguinal metastases with further follow-up. No distinction was made between superficial and invasive primary lesions in their series. Beggs and Spratt also noted significant morbidity and mortality in their series following inguinal or ilioinguinal lymphadenectomy. One of 30 patients (3.3%) died from the procedure. Significant morbidity was noted in 25 of 30 patients (83%) who underwent lymphadenectomy, with lymphedema being the most common, followed by skin slough, wound infections, lymphatic fistulae, and phlebitis. Finally, they noted that patients undergoing early lymph node dissections had survivals identical to those undergoing late lymph node dissections. Twenty-four patients underwent early lymph node dissec-

tions: 12 were considered prophylactic, nine were therapeutic, and three were performed for unspecified reasons. The six patients who underwent late lymph node dissections had palpably enlarged inguinal lymph nodes. From this group of patients, they reported on eight patients who underwent early Lymphadenectomy and had a 50% 5-year survival. Five patients underwent late lymphadenectomy and had a 40% 5-year survival. They concluded that there was no survival advantage to early lymphadenectomy and that considering the attendant morbidity and mortality of this procedure, its routine 'prophylactic' use could not be justified.

The conclusions of Beggs and Spratt are seriously flawed, however, and deserve further scrutiny. It cannot be overemphasized that it is critical to separate out those patients with superficial and invasive primary lesions, either as done in the Vanderbilt staging system or according to the TMN classification. We have demonstrated earlier in this chapter that the incidence of inguinal metastases in patients with Vanderbilt stage I primary lesions ranges from 0% to 8%, while patients with Vanderbilt stage II primary lesions have an incidence ranging from 36% to 52%. Obviously, grouping both types of patients together would cause one to doubt the efficacy of lymphadenectomy.

A second major point of concern regarding Beggs and Spratt's interpretation of their series lies in the conclusion that patients undergoing early and late lymphadenectomy have similar survivals and thus one can wait until patients with minimal inguinal lymph node involvement manifest clinically enlarged nodes to perform lymphadenectomy without sacrificing survival. This concept is inconsistent with any other tumor system that spreads primarily by lymphatic embolization. In essence, Beggs and Spratt are concluding that patients with microscopic nodal disease who are followed until their disease is obvious clinically, and then undergo lymphadenectomy, will have survivals similar to those patients who initially present with inguinal adenopathy and undergo immediate lymphadenectomy. Beggs and Spratt and simply stating that patients with similar diseases treated in a similar fashion will have similar outcomes. The reader should not find this too surprising. The real question that must be asked is whether patients with only microscopic inguinal involvement at the time of lymphadenectomy enjoy a survival advantage over those undergoing lymphadenectomy for gross nodal disease? The experience at our institution suggests that the most effective treatment for an individual with microscopic lymph node involvement is early lymphadenectomy.

Nine patients in the Vanderbilt series presented with clinical stage II disease and underwent primary lymphadenectomy. Six of nine (66%) had microscopic nodal metastases, and five of these six (83%) survived greater than 5 years with no evidence of disease. Fourteen patients with clinical stage II disease did not undergo primary lymphadenectomy. One of these 14 patients subsequently developed extensive ilioinguinal lymph node involvement, underwent lymphadenectomy, and died of his disease. Only five of the

remaining 13 patients (38%) remained free of disease for 5 years. Fifteen patients presented with inguinal adenopathy and underwent inguinal lymphadenectomy, and 10 (66%) survived 5 years. Three patients presenting with inguinal lymphadenopathy refused further treatment and all succumbed to their disease. Thus, there is at least a 17% survival advantage when lymphadenectomy is performed early.

The morbidity and mortality of ilioinguinal lymphadenectomy reported by Beggs and Spratt is also higher than our experience. No mortalities were seen in the Vanderbilt series. All 25 of our patients who underwent lymphadenectomy noted some lymphedema; however, only four (16%) thought that this incapacitated them to some degree. Three patients (12%) developed wound problems requiring a second operative procedure, and 15 (60%) developed minor wound problems that were managed by local care.

An alternative to early inguinal lymphadenectomy that has been introduced is that of the 'sentinel lymph node biopsy' first proposed by Cabanas in 1977 [11]. Cabanas performed lymphangiography via the dorsal penile lymphatics in 43 patients with penile carcinoma. He demonstrated that this lymphatic system consistently drained into a lymph node located at the anterior and medial aspect of the superficial epigastric vein, located just medial to and above the epigastric-saphenous junction. Contrast medium did not fill the deep inguinal and iliac nodes until after it had opacified this lymph node center. Forty-six patients underwent sentinel lymph node biopsy, and 15 of these were positive for metastatic carcinoma. In 12 (80%) of the patients, the sentinel lymph node group was the only group of nodes with metastatic disease, and there was not patient who had a negative sentinel lymph node biopsy and evidence of metastatic disease in other lymph nodes. Despite early optimism with this approach, multiple reports of false-negative sentinel lymph node biopsies have appeared in the literature [12–14]. Our series suggests similar problems with this approach. Six patients in the Vanderbilt series underwent sentinel lymph node biopsies; two were positive. Of the four patients with negative lymph node biopsies, two went on to develop metastatic disease in the groin. Until further studies can demonstrate an acceptable sensitivity with this approach, inguinal lymphadenectomy should continue to be the primary modality used in patients at high risk for inguinal metastases.

In summary, the available data would suggest a markedly higher propensity for inguinal metastases in patients with penile carcinomas whose primary lesions demonstrate invasive features. The Vanderbilt experience suggests that these patients will enjoy better survivals if treated by early inguinal lymphadenectomy rather than waiting until the nodes become clinically enlarged. In our experience, the benefits of lymphadenectomy more than offset thhe morbidity of the procedure in this select group of patients. The sentinel lymph node biopsy remains a conceptually interesting but unproven alternative for the management of individuals without lymphadenopathy.

Stage III penile carcinoma

There are a number of controversies in the management of patients with clinical stage III penile carcinoma. These controversies again stem from confusion between clinical and pathological staging systems.

There is no question that patients with pathologically proven inguinal metastases benefit from ilioinguinal lymphadenectomy. Table 4 contains a summary of the available literature with regard to various treatment modalities and survival in patients presenting with clinically enlarged nodes and histologically proven nodal metastases. It is obvious that inguinal lymphadenectomy is efficacious in this group of patients. Radiation therapy has little to offer, and patients do uniformly poorly without treatment. The need for aggressive surgical management of these patients assumes even greater importance when one considers that most chemotherapeutic regimens are achieving partial responses of 25% or less [16–18].

The problem with the management of patients with clinical stage III penile carcinoma is not in determining the most efficacious form of therapy for patients with histologically proven groin metastases, but rather in determining which patients have lymphatic metastases and which have only lymphadenitis. The clinical staging error is significant. Table 5 contains a summary of the available literature on the clinical staging error in patients presenting with palpable enlargement of the inguinal lymph nodes. Slightly under half of those patients with palpable inguinal lymphadenopathy will have negative lymph nodes on histologic examination.

Sentinel lymph node biopsy has been proposed to solve this dilemma as well. Fowler [12] reported his results with 18 sentinel lymph node biopsies performed on 10 patients with palpable adenopathy from squamous-cell carcinoma of the penis. Seven patients had previously been untreated, while three patients had already had their primary lesions resected (4, 21, and 24 months previously). All seven previously untreated patients underwent simultaneous surgical management of their primary lesion and sentinel lymph

Table 4. Survival according to treatment of groin nodes of patients with palpable histologically positive groin metastases

	Inguinal lymphadenectomy	Radiation therapy	No treatment
Fraley et al. [7]	4/6 (66%)	1/2 (50%)	0/1 (50%)
Fegen et al. [15]	3/4 (75%)	0/1 (0%)	—
Skinner et al. [3]	2/6 (33%)	—	—
deKernion et al. (2)	4/7 (57%)	—	0/7 (0%)
Beggs and Spratt [9]	3/5 (60%)	0/7 (0%)	0/7 (0%)
McDougal et al. [6]	10/15 (66%)	0/5 (0%)	0/3 (0%)
Totals	26/43 (60%)	1/15 (7%)	0/18 (0%)

Table 5. Error of clinical staging for clinical stage III penile cancer

		Pathologic stage	
	Total patients	Positive nodes	Negative nodes
Kossow et al. [9]	35	18	17
Edwards and Sawyers [20]	27	14	13
Hardner et al. [21]	36	21	15
deKernion et al. [2]	23	15	8
Skinner et al. [3]	10	6	4
Gursel et al. [22]	23	9	14
Fraley et al. [7]	6	4	2
Totals	160	87 (54%)	73 (46%)

node biopsy. Two of the previously untreated patients (29%) had metastatic disease in the groin. Five of their previously untreated patients had negative sentinel lymph node biopsies. Four of these remained free of tumor, while a single patient developed recurrence in the groin after a negative sentinel lymph node biopsy. All three patients with persistent adenopathy after eradication of the primary lesion had positive sentinel lymph node biopsies and underwent inguinal lymphadenectomy.

This study emphasizes two important points. The first is that sentinel lymph node biopsy has a significant incidence of false negatives. Although the numbers are small, this study suggests that this incidence is on the order of 20%. Also noteworthy is that rather than simply biopsying the 'sentinel' lymph node, the adjacent superficial lymph nodes were also sampled in most cases. The second point that this report highlights is that there is a distinct difference in the frequency of inguinal metastases in previously untreated patients compared to patients with persistence of adenopathy after eradication of the primary lesion. This point is extremely difficult to discern from the available literature, as it has not been routine to wait between treatment of the primary lesion and treatment of the inguinal lymph nodes.

Our approach has been to wait 6–8 weeks following eradication of the primary lesion before management of the inguinal nodes. All patients are maintained on a broad-spectrum antibiotic during this period to allow the lymphadenitis to subside. Clinical staging of the inguinal lymph nodes is deferred until after this waiting period. Patients with persistent adenopathy after this waiting period then undergo inguinal lymphadenectomy. Patients whose adenopathy resolves are managed according to the histologic stage of their primary lesion, i.e., patients with invasive primary lesions undergo inguinal lymphadenectomy, while those with superficial primary lesions are managed expectantly. The latter group, however, are distinctly uncommon in our experience. An additional benefit, we believe, of this approach is that it minimizes the infectious morbidities of inguinal lymphadenectomy.

Summary

In the preceding sections, the authors have presented an approach to the management of patients with squamous-cell carcinoma of the penis selected to maximize the therapeutic benefits in high-risk patients while minimizing morbidity in low-risk patients. A clinical staging system is presented in order to approach this problem in a logical fashion.

Patients with stage I penile carcinomas are all managed by eradication of the primary lesion followed by expectant management of the inguinal lymph nodes. Persistent inguinal adenopathy after treatment of the primary lesion has been a very rare occurrence in this group of patients in our experience. Patients with stage II penile carcinoma are managed by eradication of the primary lesion, 6–8 weeks of antibiotic therapy, and inguinal lymphadenectomy. The available literature suggests a high incidence of inguinal lymphatic metastases in this group of patients and supports the need for early lymphadenectomy. Finally, patients with clinical stage III disease, i.e., persistent adenopathy after eradication of the primary lesion and 6–8 weeks of antibiotic therapy, all undergo inguinal lymphadenectomy. This group is at extremely high risk and does poorly without aggressive surgical management.

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5. Recent advances and controversies in the management of Wilms' tumor

ELLEN SHAPIRO

Over the past 30 years, there has been significant improvement in the survival of patients with Wilms' tumor. Cure rates have improved due to the multitherapeutic approach to the management of the tumors. Combined surgical extirpation and chemotherapy now allow for greater than 90% survival in patients with stage I disease [1]. Chemotherapy, radiation, and second-look surgical procedures can be successfully used in patients presenting with metastatic disease or extensive local disease involving adjacent organs or bilateral renal involvement.

This review will summarize the evolution of the current approach to the treatment of Wilms' tumor. Recent advances and controversies in the preoperative evaluation and surgical management of unilateral and bilateral tumors, as well as factors relating to prognosis and relapse, tumor pathology, the late effects of therapy, and the genetics of Wilms' tumor are also presented.

Historical background and evolution of current therapy

In 1969, three cooperative groups and several independent institutions joined together to form the National Wilms' Tumor Study (NWTS) group. Two clinical trials have been completed and the data from the NWTS-3 are now available [1–4]. Over the past two decades, significant advances have been made through the efforts of this group.

The early studies determined that two-drug therapy (actinomycin D and vincristine) was superior to a single-drug regimen and that radiation therapy provided no additional benefit in stage I patients [3, 4]. Also at that time, patients less than 24 months of age and tumor specimens weighing less than 250 g were felt to be favorable prognostic factors [2]. The NWTS-2 showed that these factors were no longer of prognostic importance [5]. The early studies also defined the prognostic significance of the tumor histology [5]. Newly diagnosed patients must be staged not only clinically and pathologically, but also histologically. The two primary histologies are the *'favorable histology'* (FH) and the *'unfavorable histology'* (UH) groups. The unfavorable histology group is further defined by subdividing it into: 1) anaplastic tumors (focal or

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diffuse), 2) clear cell sarcoma of the kidney, and 3) malignant rhabdoid tumor [1, 6–8]. The NWTS-3 data continue to show that the outcome is worse for patients with diffusely anaplastic rather than focally anaplastic tumors, although the difference in outcome is no longer statistically significant [1, 6]. The clear cell sarcoma and malignant rhabdoid tumor are now viewed as distinct neoplasms rather than variants of Wilms' tumor. Malignant rhabdoid tumor is no longer being randomized by the NWTS-4 [6]. This tumor is possibly derived from multipotential cells of the infantile renal medulla with the capacity for both epithelial and mesenchymal differentiation [9]. Also, apparently identical malignant rhabdoid tumors can occur at other extrarenal sites [10]. Hypercalcemia is often present due to ectopic parathormone production [11, 12]. Brain metastases are more common than in Wilms' tumor [13]. The 2-year survival has been extremely poor. The survival at 18 months in patients with malignant rhabdoid tumors entered into NWTS-1–3 was 24% [9].

Clear cell sarcoma of the kidney, or the bone metastasizing renal tumor of childhood, is the most common unfavorable histology pattern encountered in the NWTS-3 [14, 15]. Three-year survival is 80%, and success is attributed to

Table 1. Staging system for national Wilms' tumor study 3 and 4

I. Tumor limited to kidney and completely excised

The surface of the renal capsule is intact. Tumor was not ruptured before or during removal. There is no residual tumor apparent beyond the margins of resection.

II. Tumor extends beyond the kidney but is completely resected

There is regional extension of the tumor, that is, penetration through the outer surface of the renal capsule into perirenal soft tissues. Vessels outside the kidney substance are infiltrated or contain tumor thrombus. The tumor may have been biopised or there has been local spillage of tumor confined to the flank. There is no residual tumor apparent at or beyond the margins of excision.

III. Residual nonhematogenous tumor confined to abdomen

Any one or more of the following occur:

1. Lymph nodes on biopsy are found to be involved in the hilus, the periaortic chains, or beyond.
2. There has been diffuse peritoneal contamination by tumor such as by spillage or tumor beyond the flank before or during surgery; or by tumor growth that has penetrated.
3. Implants are found on the peritoneal surfaces.
4. Gross or microscopic tumor remains postoperatively; for example, tumor cells are found at the surgical margin on microscopy of the specimen.
5. The tumor is not completely resectable because of local infiltration into vital structures.

IV. Hematogenous metastases

Deposits beyond stage III, for example, lung, liver, bone, and brain.

V. Bilateral renal involvement at diagnosis

An attempt should be made to stage each side according to the above criteria on the basis of extent of disease prior to biopsy.

a triple-drug regimen consisting of actinomycin D, vincristine, and doxorubicin (Adriamycin), since micrometastatic disease occurs early in tumor formation [14, 15]. Table 2 summarizes the results of preliminary analyses of NWTS-3 by histological type for all stages [6].

In addition to unfavorable histology, early reports showed that lymph node involvement predicted metastatic disease and relapse, while involvement of the renal vein or inferior vena cava did not significantly affect the patients' outcomes [5]. In NWTS-2, doxorubicin and postoperative radiation therapy were added to all patient groups except for stage I/FH [4]. Table 1 summarizes the current staging for patients treated according to NWTS-3 and NWTS-4 [16].

From the continued progress by the NWTS groups, we have learned that although most of the patients with anaplastic tumors have poor prognosis, those patients with stage I anaplastic tumors do not require radiation therapy and may receive the same treatment as stage I/FH and have similar excellent prognoses [1]. Also, stage II/FH who receive combination chemotherapy following nephrectomy do not need postoperative radiation therapy [6]. Furthermore, the prognosis has improved for stage III/FH when either actinomycin D, vincristine, doxorubicin, and 1000 cGy to the flank is administered or actinomycin D, vincristine, and 2000 cGy is given [1].

Finally, the addition of cyclophosphamide may improve the three-drug regimen in stage II-IV/UH, while it has not been shown to be beneficial in stage IV/FH [1]. Table 3 summarizes the preliminary data analyses for 2-year relapse-free survival and 2-year survival of patients randomized to NWTS-3 [6].

In the NWTS-4, an attempt is being made to shorten treatment regimens for all Wilms' tumor patients by decreasing the number of treatments per course and the number of treatment courses. Table 4 summarizes the NWTS-4 protocol [6].

Laboratory [17] and clinical [18] studies suggested that actinomycin D was more effective and well tolerated when administered using a single-dose schedule. A recent report indicates that severe hepatic toxicity occurred in

Table 2. National Wilms' tumor study — 3. Results by histological type (all stages)

Pathology	No. of patients	2-year relapse-free survival (%)	3-year survival (%)
I. Favorable histology (FH)	1031	88	93
II. Unfavorable histology (UH)			
A. Anaplastic tumors			
diffuse	30	51	51
focal	22	68	79
B. Clear cell	52	75	80
C. Rhabdoid	29	19	19

Table 3. National Wilms' tumor study — 3

Stage/histology/regimen	Patients	2-year relapse-free survival (%)	2-year survival (%)
I/FH/A + V: 10 wks vs. 6 mos	469	90 vs. 93	98
II/FH/± RT:* A + V vs. A + V + Adr 15 moms	262	91 vs. 90	99 vs. 93
II/FH/A + V + Adr:* O vs. 2000 cGy	262	90 vs. 91	95 vs. 96
III/FH/+ RT:** A + V vs. A + V + Adr	264	77 vs. 88	88 vs. 95
III/FH/A + V + Adr:* 1000 vs. 2000 cGy	264	82 vs. 83	92 vs. 91
Any IV + RT, any UH + RT: A + V + Adr vs. A + V + Adr + C	291	63 vs. 69	78 vs. 80

A = actinomycin D, C = cyclophosphamide, V = vincristine, Adr = Adriamycin (doxorubicin), cGy = centiGray, 1 cGy = 1 rad.

* Comparison is for the collapsed regimens from the factorial design. Persistent disease at last follow-up in stage IV patients is scored as relapse.

five nonirradiated patients treated with vincristine and single-dose actinomycin [19]. Since this report, hepatotoxicity with the standard regimen has also been noted. Although the NWTS-4 has reduced the single dose of actinomycin D, the exact etiology of the hepatotoxicity remains unclear, and further evaluation of other possible factors or drug interactions are being investigated.

Preoperative evaluation

Diagnosis of Wilms' tumor can be strongly suspected in a child with an asymptomatic abdominal mass that is found to be intrarenal on intravenous pyelogram (IVP) [20]. Preoperative radiographic evaluation must assess the function of the contralateral kidney, renal vein, and inferior vena caval involvement, and the presence of pulmonary metastases. An IVP or CT scan of the kidneys with contrast is acceptable to evaluate contralateral renal function and possible bilateral tumor involvement. A CT scan may be more sensitive in detecting the extent of local invasion of the primary tumor. Also, small tumor foci in the contralateral renal unit may be detected by CT scan [21]. Although sonography of the kidneys cannot be substituted for the IVP or contrast-enhanced CT, it is a useful, noninvasive method for the preoperative detection of tumor thrombi in the renal vein and the inferior vena cava [21]. When the inferior vena cava is not well visualized, an inferior vena cavagram is performed. If there is occlusion of the inferior vena cava, superior vena cavography and right atrial catheterization are indicated [23]. Although renal vein and inferior vena caval involvement will be diligently

Table 4. National Wilms' tumor study — 4 protocol

Disease	Initial therapy	Radiotherapy	Chemotherapy regimen[a]
Stage I/favorable histology, I/anaplastic	Surgery	None	EE-actinomycin D plus vincristine (24 weeks) EE-4-pulsed, intensive actinomycin D plus vincristine (15 weeks)
Stage II/favorable histology	Surgery	None	K-actinomycin D plus vincristine (22 and 65 weeks) K-4-pulsed, intensive actinomycin D plus vincristine (24 and 60 weeks)
Stage III/favorable histology	Surgery	1080 cGy	DD-actinomycin D vincristine and doxorubicin (26 and 65 weeks) DD-4-pulsed, intensive actinomycin D, vincristine and doxorubicin (24 and 52 weeks)
High risk (clear cell sarcoma, all stages) and stage IV/favorable histology	Surgery	Yes[b]	DD-actinomycin D, vincristine and doxorubicin (26 and 65 weeks) DD-4-pulsed, intensive actinomycin D, vincristine and doxorubicin (24 and 52 weeks)
Stage II–IV/unfavorable histology	Surgery	Yes	DD-actinomycin D, vincristine and doxorubicin (26 and 65 weeks) J-actinomycin D, vincristine, doxorubicin, and cylophosphamide (65 weeks)

Data reproduced with permission [6].

[a] Refer to latest National Wilms' Tumor Study protocol for dosage and length of treatment.

[b] Clear cell sarcoma patients receive 1080 cGy, and stage IV/favorable histology patients are given 1080 cGy if the primary tumor would quality as stage III were there no metastases.

evaluated in the patient with a nonvisualizing kidney, each patient needs to be adequately studied preoperatively since fewer than 10% present with signs or symptoms to indicate intravascular tumor extension. [23]. A chest roentgenogram evaluation including PA, lateral, and both obliques is recommended [6]. CT scan of the lung is a useful adjunct to elucidate plain film findings. Also, CT has been used to detect pulmonary lesions in the absence of plain film findings. A recent study identified 11/124 patients with Wilms' tumor who had positive pulmonary CT scans despite normal chest roentgenograms [24]. All patients had favorable histology, and, excluding the CT finding, most (7/22) were stage III. Those 11 patients were staged and treated according to the

abdominal stage. Four of 11 (36%) relapsed and all recurrences were pulmonary. Since there is an appreciable percentage of false-positive findings of densities found only on the CT scan, lung biopsy may be advisable to avoid overtreatment (stage IV) in this group of patients. Findings on CT despite a negative chest roentgenogram should not be ignored, since granulomas are not commonly found in the pediatric population. Hepatic CT evaluation is only mandatory in NWTS-4 when liver metastases are found at laparotomy and therapeutic response needs to be monitored [6]. These are protocol requirements and are not necessarily for general use.

Finally, cystoscopy and retrograde pyelography should be performed prior to nephrectomy to evaluate patients with hematuria or nonvisualization of the kidney. Ureteral, bladder, and urethral metastases have been reported [25–28]. Invasion of the renal pelvis or ureter would also alter the surgical approach and would necessitate nephroureterectomy [29]. Cystoscopy and retrograde studies should also be performed to visualize the ureteral remnant in a child who has undergone previous nephrectomy for Wilms' tumor and subsequently develops hematuria.

Surgical advances

Over the past decade, surgery has continued to be the mainstay in the treatment of Wilms' tumor. The transabdominal transperitoneal approach permits careful staging of the disease during radical nephrectomy. Complete abdominal exploration must be performed, and complete mobilization and inspection of the anterior and posterior surface of the contralateral kidney with biopsy of suspicious areas are mandatory. Although formal hilar and periaortic lymph node dissection is not recommended by the NWTS-4 protocol, lymph node sampling is important for accurate staging. If the site of an abnormal node is outside the field for flank irradiation, a metal clip should be used to identify this area. Also, if the patient appears to be a surgical stage I or II, sampling from the iliac, periaortic, and celiac nodal areas may reveal occult nodal involvement. Following this, a local-regional stage is given to the tumor by the surgeon based solely on the intraoperative findings [6].

Although preoperative evaluation of the renal vein and cava is essential, intraoperative palpation of the vein is also important prior to the ligation of the vessel. Surgical technique for removal of intravascular thrombus extension has been reviewed [22]. During removal, the surgeon should note whether the thrombus is attached to the intima or whether it penetrates the vessel wall.

Intracardiac extension (ICE) has recently been reviewed by the NWTS [23]. If the tumor thrombus can be removed intact and without embolization, the patient is a stage II in the absence of nodal disease or distant metastases. Intracardiac extension occurred in 15 of 2280 patients (0.7%). Only one had cardiac symptoms preoperatively. Six children had ICE diagnosed preoperatively, while preoperative vena cavagram, CT, and ultrasound did not detect

ICE in five and was not performed in four patients. In the latter four children, ICE was only recognized postoperatively. Cardiac pulmonary bypass was required in 10 patients. Eleven of the 14 children with FH survived (2-year survival rate of 86%). This study reiterates the importance of accurate preoperative clinical staging and that ICE should be suspected in patients with extensive venal caval thrombus or who have cardiac symptoms or decompensation during examination or surgery. The presence of ICE does not portend a grave prognosis. Cardiopulmonary bypass with hypothermia for removal of a Wilms' tumor with ICE has been reported [22].

Other recommendations for the surgical management of patients with Wilms' tumor include adrenalectomy if the tumor mass arises from the upper pole of the kidney. The adrenal gland may be left in place if it is not abutting the tumor. This issue is most important in patients with bilateral Wilms' tumor undergoing second-look operations [6, 39].

If the tumor has invaded contiguous viscera, radical excision is advised only if all of the tumor can be completely removed. Also, it is important to determine the extent of peritoneal soilage of tumor for accurate surgical staging. This may occur at the time of biopsy, tumor removal, or possible preoperative or perioperative tumor rupture. If the tumor cell spread is local, the patient is considered stage II (no radiation therapy), but when there is diffuse peritoneal spillage, the patient is considered stage III and radiation therapy is delivered to the entire abdomen and pelvis. Specific guidelines are outlined by the NWTS-4 protocol to determine staging in each of these instances [6].

The use of preoperative chemotherapy in the treatment of patients with intravascular extension or inoperable tumors remains controversial. The use of preoperative chemotherapy is not new for bulky unilateral disease. In 1970, Weggert and Koop [30] reported a marked decrease in size of inoperable Wilms' tumors in 12 patients who received preoperative chemotherapy and radiation therapy. Bracken et al. [31] reported similar success in 16/19 patients with large inoperable Wilms' tumors who received preoperative actinomycin D and vincristine. Recently, Kogan et al. [32] described three patients with presumed Wilms' tumor who had intravascular thrombus extension. Preoperative chemotherapy and radiation therapy were administered. This resulted in a marked reduction of intravascular tumor volume or complete eradication of the tumor, which facilitated subsequent surgical extirpation. Bray et al. [33] reported a brief pretreatment course in four patients with large bulky tumours with intravascular invasion. Prior to therapy, tissue was obtained by fine-needle aspiration biopsy in three patients and open biopsy in one. According to the NWTS-4, fine-needle aspiration biopsy by an anterior route is considered to be *'diffuse peritoneal soilage'* and using a posterior approach is considered to be *'local soilage'* [6]. The diagnostic impact of such biopsies is unknown since this has not been standard therapy in the past. Also, although preoperative chemotherapy reduces the size of the tumor and may render it resectable, this approach has not resulted

in improved survival rates [34]. Preoperative chemotherapy does result in the loss of important staging information, which may reflect the inherent aggressiveness of the malignancy. Regardless of the intraoperative staging that occurs at approximately 6 weeks following diagnosis and pretreatment with doxorubicin and vincristine, all patients are considered stage III and therefore receive additional therapy [37]. This practice stems from the experience in SIOP-6 [35], where patients receiving preoperative chemotherapy randomized to not receive radiation relapsed more frequently below the diaphragm than patients receiving radiation. To help prevent these recurrences, routine postoperative radiation therapy is advocated by the NWTS. SIOP, instead, has added an Adriamycin congener to the treatment regimen in all patients with at least postoperative stage II [37]. Therefore, many stage II children (10–15%) may receive a potential cardiotoxin unnecessarily, which seems in part to negate the advantage of preoperative chemotherapy in an attempt to avoid adjuvant radiation therapy [37].

Other concerns surrounding the pretreatment of tumors with chemotherapy include the ability to obtain adequate tumor tissue in order to distinguish Wilms' tumor from other small, round-cell tumors. It is improtant to remember that, despite advances in the preoperative radiographic evaluation of these patients, there continues to be a 1.5% error rate in the diagnosis of renal masses in children [1]. Benign lesions were represented among the misdiagnoses. There is further concern whether preoperative chemotherapy can alter the tumor histology and result in cellular atypia and pleomorphism that may be later interpreted as anaplasia. Zuppan et al. [38] showed that in 140 patients with unilateral Wilms' tumor receiving preoperative chemotherapy, anaplasia was confirmed in nine patients (6%). The incidence of anaplasia did not appear to be increased in patients receiving preoperative chemotherapy. When anaplasia is found in this setting, it should be considered to have the same implications as when it is diagnosed in an untreated lesion. It is important to note that the initial biopsy failed to reveal anaplasia in 7/11 cases with demonstrable anaplasia at resection. This finding may reflect a preoperative sampling error or, less likely, the development of true anaplasia following chemotherapy.

Changes in the therapeutic approach to bilateral Wilms' tumor are evolving. The frequency of synchronous bilateral tumors (stage V) is 4.4%. Despite advances in diagnostic radiology, only 64% of the contralateral lesions were found preoperatively, again emphasizing the importance of intraoperative examination of the contralateral kidney [39, 40]. Anaplastic histology in bilateral disease is 10%, which is more than that found in unilateral Wilms' tumors (4.5%) (Table 2). Also, 4% of bilateral patients have been shown to have discordant histology, which again underscores the need for visual inspection and palpation of suspicious lesions [39]. Recommendations for the management of these patients have been outlined by Blute et al. [39]. Briefly, they recommend excision of the tumor if it can be completely removed leaving sufficient renal parenchyma for normal renal function. This is not usually

possible, and bilateral biopsy and staging is performed with biopsy of suspicious lymph nodes. Chemotherapy with vincristine and actinomycin D is instituted. After completion of chemotherapy, a second-look operation is performed if there is persistent but resectable tumor or if gross tumor was present after the first surgical procedure and the tumor appears to have responded on radiographic reevaluation. At second-look laparotomy, a radical nephrectomy is performed on the more extensively involved kidney, providing partial nephrectomy or tumorectomy from the less-involved kidney leaves a satisfactorily functioning renal unit. If gross or pathologic evidence of persistent disease is present, the patient should receive radiation therapy to the kidney(s) and doxorubicin is added to the chemotherapy regimen. If the surgical procedure shows no gross or pathologic evidence of persistent disease, the drug regimen, including actinomycin D and vincristine, is continued for a total of 65 weeks.

Factors relating to relapse in patients with stage I/FH

The importance of tumor histology has been determined in previous NWTS, and patients with stage I/FH have an excellent prognosis. Twenty-four patients with stage I/FH relapsed on NWTS-3 and were compared with 48 matched control subjects who had not relapsed for at least 2 years after diagnosis [41]. Twenty-three patients developed distant metastases and one patient had only a local recurrence. The pathological specimens were reviewed and microsubstaging was developed and found to be of prognostic importance. Four histologic features relating to the degree of tumor extension within the involved kidney were defined. These histologic features were: 1) invasion of the tumor capsule with tumor cells in the perirenal fat, 2) presence of an 'inflammatory pseudocapsule' due to granulation tissue and an inflammatory infiltrate in the perirenal soft tissue at the surface of the kidney, 3) renal sinus invasion, and 4) tumor in intrarenal vessels. No patient who relapsed had negative microstages. With these new pathological observations, consideration may be given in the future to nephrectomy only in stage I/FH patients with negative microstaging. Careful evaluation of the renal sinus is important and calls for upstaging the tumor to stage II, or stage III if there is involvement of the surgical margin [37].

Prognosis for patients with metastatic disease at diagnosis

Early reports from the NWTS reported that anaplastic or sarcomatous histology and regional lymph node involvement were of particular importance in predicting relapse in patients who did not present with metastatic disease at diagnosis (stage I–III) [5]. Operative spillage and residual abdominal tumor after exploration were also thought to be associated with a high risk of

abdominal recurrence. Since only 12% of all patients entered into the study are stage IV, it is only now that sufficient knowledge is available regarding prognostic factors from the compiled NWTS protocol results (1969–1983) [42].

Age at diagnosis has been correlated to the presence of metastatic disease. Metastases are more likely to be present in older children (greater than 6 years, 24%) than infants (less than 1 year, 1%) [42].

Patients with regional spread within the abdomen, ranging from microscopic tumor in the surgical margin to gross residual, had a twofold increase in the risk of having distant metastases when compared with those having disease confined to the kidney. When there was lymph node or renal vasculature involvement, the risk was increased threefold. In fact, 47 of 100 patients with lymph node and renal vein or inferior vena caval involvement at diagnosis had liver or lung metastases [42].

Survival of patients with stage IV disease was adversely affected by anaplastic histology, sarcomatous histology, abdominal spread (nonresectable tumor invading peritioneum or other abdominal organs), and operative spillage. Tumor death at 2 years after diagnosis for patients with stage IV/FH decreased from 29% in earlier studies to 9% in the NWST-3 as a result of improved therapeutic regimens. These results for stage IV/FH are now comparable to those stage III patients with nonresectable local invasion at diagnosis. Long-term survival for stage IV/UH remains dismal at 17%. Lymph node involvement, although significant in predicting metastatic disease, is not important in predicting survival in patients with stage IV and does not predict abdominal recurrence in patients without metastatic disease [42].

The temporal relationship of the development of metastatic disease (lung/liver) in patients with favorable histology has also been shown to be important. When metastases develop after treatment, 4-year survival rates were significantly decreased (47%) when compared to those presenting with stage IV/FH at diagnosis (72%). This factor did not affect the poor prognosis of the stage IV/UH group. Also, when one examines the extent of initial pulmonary metastases at diagnosis, there is no significant difference in outcome in those patients with a single pulmonary nodule, multiple unilateral nodules, or bilateral disease involvement [42].

Recently, Thomas et al. [43] examined the prognostic significance of attachment, invasion, or metastases to the liver at diagnosis (stage IV). They showed that the overall 4-year survival in NWTS-3 was similar for stage II and III (89% and 85.5%, respectively), and 81% for stage IV. This would infer that hepatic attachment/invasion did not worsen the prognosis in stage II or III and that aggressive therapy for stage IV has improved the prognosis for liver metastases at diagnosis. There is no difference in survival if one's metastatic disease is present in the liver and/or lung versus lung only. The only effect of metastatic sites is in those patients who develop liver metastases during or after therapy, who then carry a very bad prognosis [42].

Nephroblastomatosis

The NWTS Pathology Center, under the guidance of Dr. J. Bruce Beckwith, has been working diligently to further understand the pathological findings of nephroblastomatosis [14, 37]. The term *nephroblastomatosis* is applied to those specimens with persistent embryonic remnants (persisting after 36 weeks gestation) or nodular renal blastema that become confluent, invasive, or cause massive enlargement of the kidney. More recently, nodular renal blastema has been termed *nephrogenic rests* and are presumed precursors to Wilms' tumor. Multiple or diffuse nephrogenic rests is termed *nephroblastomatosis*. Although most Wilms' tumor are unilateral, there are many unilateral, multicentric tumors, suggesting that these kidneys have multiple precursor lesions. The nephrogenic rests are identified in 25–40% of kidneys with Wilms' tumor. Recently, a new classification of these lesions has been proposed [14, 37]. Nephrogenic rests that are found peripherally in the renal lobe are termed *perilobar nephrogenic rests*. Lesions occurring deeper in the cortex, within the medulla, or renal sinus are termed *intralobar nephrogenic rests*. These nephrogenic rests have varied pathological potential and may remain dormant as blastema, become hyperplastic rests, develop into nephroblastomatosis or sclerose, involute, and completely regress. Most important, though, is the increased risk of Wilms' tumor in the contralateral kidney when either intralobar or perilobar nephrogenic rests are found in the resected kidney of a child with unilateral disease. Metachronous lesions were reviewed from NWTS-2 and were found to occur in 5% of the cases with perilobar nephrogenic rests and in 60% of the ipsilateral tumors with intralobar nephrogenic rests. The significance of nephrogenic rests in nontumorous kidneys is not completely understood. Nephrogenic rests are found as perilobar nephrogenic rests in about 1% of newborn autopsy specimens. Since 1 in 10,000 newborns will subsequently develop a Wilms' tumor at some time during the childhood years, then only about 1% of infants with foci of perilobar nephrogenic rests do so. Recently there has been a great deal of controversy about the management of the multicystic dysplastic kidney and poorly functioning, obstructed, dysplastic upper pole segment of duplex kidneys, since nephrogenic rests have been incidentally identified in some of these specimens [44]. Beckwith [45] proposed the statistics that if 5/100 dysplastic kidneys have nephrogenic rests and 1/100 infants with rests develop a Wilms' tumor, 2,000 nephrectomies would need to be performed in this setting to prevent the development of a single Wilms' tumor. A tumor registry for multicystic dysplastic kidneys has recently been organized so that the incidence of this pathological finding and subsequent pathology in the contralateral kidney can be determined, since Wilms' tumors have developed in multicystic dysplastic kidneys [44]. The tumor registry, which will include multicystic dysplastic kidneys managed nonoperatively, will provide further information about the malignant potential of these nonfunctioning kidneys.

Patients with nephroblastomatosis found in association with unilateral

Wilms' tumor are at increased risk for the development of a contralateral Wilms' tumor. For this reason, ultrasound follow-up every 3 months is recommended. This recommendation is also given to patients who during routine exploration for unilateral Wilms' tumor have individual rests or nodules of nephroblastomatosis in the contralateral kidney. Postoperative therapy is administered according to the stage of the primary tumor with close imaging follow-up [14].

Long-term effects of therapy for Wilms' tumor

There have been many excellent reviews of the late effects of treatment for Wilms' tumor [46–48]. These reviews have examined both the acute and late complications of surgery, chemotherapy, and radiation therapy. Emphasis has been placed on the importance of long-term follow-up to determine tumor recurrence, damage to normal tissues and organs, the development of secondary malignant neoplasms, and the overall assessment of the quality of life. Two-year relapse-free survival or 5-year survival from nephrectomy is considered a curative period for a patient with Wilms' tumor [49]. Almost all recurrences occur within 2 years of nephrectomy, but cases of recurrence are reported as late as 11 years after the initial diagnosis [50]. With improved long-term survival, attention is now turning to the effects of therapy on normal tissues. Patients with right-sided Wilms' tumor treated with chemotherapy with or without radiation therapy can develop acute liver toxicity, which occurs within the first weeks following therapy [51]. In most cases, the liver damage causing the syndrome of hepatomegaly, abdominal distention, and ascites is reversible [46, 49]. In addition to acute toxicity, chronic liver dysfunction with portal hypertension with or without mild cirrhosis has been reported in patients with right-sided tumors. When hepatic histopathology was available, it appeared to be unrelated to the patient's radiation status [52].

The adverse skeletal effects of megavoltage irradiation have been studied and appear to be as frequent, but less severe, than orthovoltage irradiation [47, 49]. Radiation to the axial skeleton, pelvis, and thorax can result in kyphosis, scoliosis, unilateral pelvic hypoplasia, and hypoplasia of the hemithorax. A high incidence for scoliosis (54%) has been reported in one series, although functional disability was minimal, with only 3/14 developing symptoms. In this study, neither dose nor age were found to be significant in predicting the development of scoliosis [46].

The long-term effects of therapy on renal growth and function have been recognized over the past 10 years. It has been thought that low-dose irradiation (not exceeding 1500 cGy administered with actinomycin D) may affect the rate of compensatory hypertrophy of the remaining renal unit following nephrectomy for Wilms' tumor. The renal function in these patients does not appear to be adversely affected. Progressive renal insufficiency may

be seen after the administration of 2000 cGy [53], and radiation nephritis has been reported 20 years after the administration of 1400 cGy to the kidney [54]. In 1986, a study comparing the size and function of the solitary kidney in patients undergoing nephrectomy for Wilms' tumor and hydronephrosis was reported [55]. All patients were nephrectomized for Wilms' tumor and received actinomycin D and abdominal radiation with the solitary kidney exposed to 500–1500 cGy. The kidney was enlarged in both the hydronephrosis group (1.2%) and the Wilms' tumor group (1.25%) but was significantly greater in those with hydronephrosis, despite their somewhat older average age at nephrectomy (7.9 ± 1.2 years versus 2.6 ± 0.4 years). The Wilms' tumor group had serial IVPs, and it appears that renal compensatory growth was blunted during the first 2 years following therapy. Although IVPs were not serially available in the group nephrectomized for hydronephrosis, a significant increase in growth was noted during the first 2 years following nephrectomy in a similar group of patients previously reported. Also, glomerular filtration rate was 92% of the normal control in the hydronephrosis group and 82% of the controls in the Wilms' tumor group.

A more recent study of renal growth in patients nephrectomized for Wilms' tumor and patients with congenital solitary kidney due to unilateral renal agenesis has been reported [56]. Most patients with Wilms' tumor received radiation therapy (2500–4000 cGy) and chemotherapy. Ultrasound was used to detect increases in parenchymal thickness. In the renal agenesis group, the solitary kidney achieved 188% of the volume of the normal kidney within 4 years of life and normal growth continued thereafter. A similar increase (180%) was seen in the remaining kidney in patients nephrectomized for Wilms' tumor, with an increase seen 2–4 years after nephrectomy. If the nephrectomy was in a child less than 4 years of age, this renal growth was seen within 2 years.

The incidence of second malignant neoplasms in survivors of Wilms' tumor has been recently reported from NWTS [57]. The 1% incidence of second malignant neoplasms observed in these patients at 10 years after diagnosis is very similar to previous reports [58, 59]. Preliminary reports suggest that these second malignancies may increase rapidly after 10 years. This data again is similar to estimates (6% and 8.5%) from previous analyses of survivors at 20 years [59, 60]. The spectrum of second malignant neoplasms includes a preponderance of myeloid leukemias, sarcomas, and carcinomas, but osteogenic sarcoma, retinoblastoma, and hepatocellular carcinoma have also been reported. In all but two patients developing second malignancies, radiation therapy was administered but cannot as yet be cited as the single causal factor. Future follow-up studies in survivors developing second malignant neoplasms will be important, as fewer patients are now receiving radiation therapy and lower drug dose schedules are being administered.

Li et al. [61] reported on the outcome of pregnancy in survivors of Wilms' tumor, most of them (114/191) in women who had receive abdominal radiation. An adverse outcome occurred in 34 (30%), including 17 perinatal

mortalities and 22 low birthweight infants. These figures were significantly higher than those in a similar group of pregnancies in U.S. white females. There were no perinatal deaths in 77 pregnancies in nonirradiated women, nor were there any in the wives of male patients who did receive radiation therapy. There were two (3%) low birthweight infants born to fathers with Wilms' tumor who had received radiation therapy. From this study, radiation therapy cannot be cited as the absolute causal factor. Nonetheless, women with a history of Wilms' tumor and irradiation should be counseled regarding the risks associated with their pregnancies, bearing in mind there is no evidence from this study and others that there is an increase in congential anomalies in the offspring of individuals treated for Wilms' tumor [62].

Genetic aspects of Wilms' tumor

During the past two decades, there has been a great deal of cytogentic and molecular data supporting the notion of a heritable and nonheritable subgroup of Wilms' tumor patients. In 1972, Knudson and Strong suggested that Wilms' tumor may result from a series of two cellular genetic events [63]. The nonhereditary form of Wilms' tumor may result from two postzygotic (somatic) events in a single cell. In the heritable form, the first mutation would occur as a prezygotic (germinal) event and would be present in all cells. Therefore, a single second event or mutation in any target tissue may lead to the development of a tumor. This model could explain the earlier age (1.8 years) [64, 65] at which familial cases occur and also the increased incidence of bilateral and multicentric tumors in familial cases.

The frequency of bilateral disease has been shown to be 21% in hereditary cases, and the penetrance or probability that a gene carrier for the Wilms' tumor mutation will develop overt tumor was approximately 63%. Knudson and Strong [63] estimated that approximately 40% of all Wilms' tumor cases resulted from a germinal mutation and were heritable. Recent epidemiological reviews report a lower (4%) overall prevalence of bilateral tumors [66–68], and the frequency of heritable Wilms' tumor may be about 20% [69]. Nevertheless, these observations suggest that all bilateral cases of Wilms' tumor and many unilateral cases are the result of a germinal mutation and support the two-step mutational model.

Many theories have been proposed to explain the genetics of Wilms' tumor [70] since the two-step mutational model does not explain Matsunaga's observation of the high frequency of Wilms' tumor in two or more offspring whose parents are unaffected [64]. The inherited pattern in these kindred is felt to be autosomal dominant with incomplete penetrance, although this explanation may not completely account for this occurrence.

The association of various congenital anomalies with Wilms' tumor has been confirmed in surveys conducted with the National Wilms' Tumor Study. The most frequent malformations include congenital aniridia [65, 71, 72],

hemihypertrophy [65, 67, 71, 72], and genitourinary malformations [65, 67, 71, 72]. Studies confirm that 1.0–1.5% of patients with Wilms' tumor have aniridia, which is almost always the sporadic type [72]. Other congenital anomalies have been found with increased frequency in association with aniridia and Wilms' tumor, including genitourinary anomalies, mental and growth retardation, facial anomalies, and other defects. This group of anomalies is cumulatively referred to as the WAGR (*W*ilms' tumor, *A*niridia, *G*enitourinary abnormalities, *R*etardation) syndrome. Sporadic aniridia is the most consistent component of the syndrome, and Wilms' tumor occurs in about 33% of these cases. Also, about 3% of the patients with Wilms' tumor have hemihypertrophy [65, 68]. In addition, hemihypertrophy is sometimes seen in the Beckwith–Wiedemann syndrome, and this syndrome has a 6% incidence of Wilms' tumor [73]. Lastly, genitourinary anomalies are found in about 5% of patients with Wilms' tumor [65, 67, 71, 72]. These include renal dysplasia, horseshoe kidney, collecting system anomalies, pseudohermaphroditism, hypospadias, and cryptorchidism [70].

The aniridia and Wilms' tumor complex may be consistent with the heritable form of the tumor, since the tumors associated with this complex develop at an earlier age and there is an increased frequency of bilaterality. In support of this observation is the finding that 33% of the patients with sporadic aniridia and Wilms' tumor have a constitutional chromosomal anomaly that has been localized to the short arm of chromosome 11 band 13 (11p13) [74–76]. According to the two-step mutational model, this deletion would represent the first event or mutation, and it would follow that the incidence of Wilms' tumor in these patients would be increased, as well as the frequency of bilateral disease. All patients with chromosome 11p13 deletions had aniridia. A variable degree of mental and growth retardation was present and 33% developed Wilms' tumor.

Constitutional chromosomal anomalies include chromosomal deletions, translocations, and reduplication [77]. In addition, Riccardi [78] has reported two unrelated patients with aniridia/iris dysplasia and Wilms' tumor who had a normal chromosomal complement, suggesting a submicroscopic deletion or mutation affecting both loci.

Constitutional subband deletion is also associated with the altered expression of other genetic loci. These genetic loci associated with the short arm of chromosome 11 have been examined to determine their possible correlation with the aniridia–Wilms' tumor complex [70]. Due to the close proximity of the catalase gene, this locus has been consistently correlated with deletions involving 11p13 [79–82]. Some of these patients with the aniridia Wilms' tumor complex have half the normal level of catalase. At this time, there are no other consistent genetic loci mapped to the short arm of chromosome 11 that have a strong association with Wilms' tumor. As advances occur in recombinant DNA techniques and chromosome mapping, further information is becoming available about the hereditary predisposition to Wilms' tumor. Compton et al. [85] examined the relationship between genetic alterations

at chromosomal band 11p13 and the WAGR syndrome. They reported the identification of 15 new 11p13-specific DNA probes, which have been used to subdivide the chromosome band intervals using DNA from WAGR patients with various constitutional deletions of 11p13. Also, a physical map of this region of the genome was constructed using infrequently cutting restriction enzymes and pulsed field gel electrophoresis. Furthermore, this map localized the specific DNA fragments that most likely contain the genes for Wilms' tumor and aniridia.

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6. Alternative forms of urinary diversion after cystectomy

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Urinary diversion

Any operation designed to redirect the urine after cystectomy should both be clinically acceptable to the surgeon, and socially and psychologically acceptable to the patient. It must be oncologically appropriate and consider patient survival, anticipated cancer morbidity, possible mechanisms of tumor spread in the pelvis, and the risks to the patient from procedures that often require revision operations. Likewise, patient motivation and aptitude, physical and neurologic disability, and social factors influence the selection of urinary diversion.

The ideal urinary diversion should mimic bladder function as closely as possible; it should achieve a low-pressure, capacious reservoir to collect and store urine, achieve continence and allow voluntary control of the expulsion of urine, and should avoid significant fluid and electrolyte shifts. The current continent diversion and orthotopic bladder replacement techniques are approaching these goals, and the resurgence of interest in them and innovative technological advances have considerably improved their acceptance, but the ideal procedure has yet to be developed.

Bricker's description of the appliance-dependent urinary ileostomy introduced a new area of acceptability of radical pelvic surgery in the 1950s [1]. However, poor long-term results, particularly in patients with long life expectancies, soon led to disillusionment with this procedure and heralded the current popularity of continent urinary diversion operations. Nonetheless, the Bricker procedure is still the most widely used form of urinary diversion after cystectomy and remains the standard to which all other diverting procedures must be compared, particularly as continent diversions have had insufficient time to show the development of long-term complications or drawbacks.

Continent diversions can improve the quality of life after cystectomy, facilitate psychologic adjustment, and ease concerns over body image, a factor that might otherwise delay patients in dealing with malignancy. Patient awareness of the continent alternative has spread by word of mouth, by the media, through ostomy associations, and through the requirement that all

Lepor H. and Ratliff T.L. (eds), Urologic Oncology.

surgical alternatives be discussed with patients. This has prompted the urologist to view the development of continent diversion seriously. But emotional factors aside, social and economic considerations may also dictate a need for continent diversion, particularly in countries where the social rejection of a wet stoma and the cost of ostomy appliances preclude the use of an ileal conduit. Unfortunately, these procedures are far more complex and have a higher complication rate than the standard ileal conduit, and their use should probably not be in the surgical repertoire of the occasional surgeon [2].

Patient selection

Urinary diversion of any type is becoming a less common operation than in the past, when intractable voiding symptoms, incontinence, and upper tract deterioration due to bladder dysfunction were managed by diversion. Currently the leading indication is for patients undergoing an extirpative procedure for pelvic malignancy. In addition, some patients with appliance-dependent urinary diversion who cannot be undiverted to the native bladder due to prior cystectomy may elect conversion to a dry stoma because of improved personal and social acceptance.

There are several important considerations in continent urinary diversions. Since all of the available procedures require resection and mobilization of a considerable length of bowel, anatomic and pathologic factors regarding the ileum, ileocecal segment, right colon, or sigmoid colon may preclude continent diversion. These include nonavailability of an appropriate bowel segment because of prior bowel resections, extensive intestinal adhesions, bowel pathology such as ulcerative colitis and Crohn's disease, and a short, fat, or diseased mesentery, which may limit bowel segment mobilization and remodeling. Often selection of the most suitable diversion for a particular patient may rely on intraoperative findings and on which bowel segments seem to work best.

Resection of a considerable length of intestine can alter bowel habit, but unlike patients with neurologic dysfunction, cancer patients tend to have fewer bowel problems. Intestinal malabsorption may, however, contraindicate and complicate continent urinary diversion.

In some cases prior abdominal or pelvic radiotherapy may mitigate against continent diversion, especially when prior surgery has fixed the bowel in the radiation field. In many respects continent diversions must withstand more stress and require greater pliability than the standard ileal conduit, and irradiated bowel may serve as a poor candidate, although Skinner has found carefully selected cases to be relatively complication free [3].

Offering these procedures to patients with a poor prognosis following resection of their malignancy is inappropriate, as the complexities of these procedures add to patient morbidity, and if revision is later required, it may be on a patient who is terminally ill and not a surgical candidate. In the extremely elderly patients or the infirm, there is often wisdom in not offering

continent diversion or even extirpative surgery. In general, younger patients who are healthier or image-conscious, and are better candidates for possible revision, are more suited for continent diversion.

Social and physical considerations are also important. Patient motivation and intelligence is necessary to manage a diversion that requires active participation, as is physical ability to operate the sphincter mechanism, whether it be neurologic control of the native sphincter or dexterity to perform self-catheterization or operate an artificial urinary sphincter.

Potential for cancer spread to the urethra, as in advancing transitional cell carcinoma, is a relative contraindication to formation of a reservoir connected to the urethral sphincter, and patients with a compromised or weak sphincter will suffer incontinence from contractions in the reservoir that may overcome urethral resistance.

The complexity and potential for early and late complications demand that patients be counseled carefully preoperatively, for a considerable number of patients will decline a continent diversion in lieu of an ileal conduit based on an honest report of the duration of surgery and hospitalization and the incidence of early and late complications. This drop-out rate is certainly better than dealing with an unhappy, poorly informed patient who may later encounter problems.

Preoperative radiographic studies should include excretory pyelography and bowel contrast studies in those patients who have suspected bowel pathology or significant prior abdominal surgery. Patients in whom continent diversion is selected who are poorly nourished may require a period of preoperative hyperalimentation. A mechanical bowel prep, such as with polyethylene glycol electrolyte intestinal lavage, and an antibiotic bowel prep are accompanied by intravenous fluids to avoid preoperative dehydration.

Systems of urinary diversions

Urinary diversion can be accomplished by an incontinent-appliance-based system, a catheterizable stoma and reservoir technique, or formation of a neobladder using the native urethra as an outflow tract. The decision on how best to divert a patient depends on the best match of the advantages and drawbacks of each type of diversion when individualized for the patient. The plethora of operations available for diversion attests to the reality that no perfect diversion exists.

Appliance-dependent urinary diversions

Ileal conduit urinary diversion

For over 30 years, thhe ileal conduit has been the standard method of long-term urinary diversion after cystectomy [4]. Before this time, several other

means of diversion were in favor, such as the skin-flap ureterostomy [5], the tunneled ureterosigmoidostomy [6, 7], and the rectal bladder [8]. Finally, Bricker [1], in 1950, described ureteral implantation into a small intestinal segment to a stoma and external urinary appliance. Though several minor modifications have been described [9, 10], no major changes in this technique have occurred since its inception.

In the presence of prostatic or bladder malignancy when relatively short-term palliation may be the goal, the ileal conduit may be the primary choice. It is a technically simpler procedure than a continent diversion, with a significantly shorter operating time. In our institution an assessment of a cancer patient's adaptability, survivability, functional capabilities, and motivation generally leads to ileal conduit diversion in older patients and in younger patients with advanced disease.

Advantages include the fact that urinary stasis and reabsorption are minimized, a shorter length of bowel is required, and a healthy segment can be selected, even after pelvic irradiation. There is no need for catheterization, and there is no sphincter requirement, which is the area of most continent diversion problems.

However, many ileal conduit problems are potentially serious. Most patients are chronically bacteriuric, and this may lead to the 18% rate of pyelonephritis, and the 12% to 30% incidence of renal damage reported [11–13]. Over many years of follow-up, stomal stenosis occurs in 4% to 6% of patients, and segmental or full-length stenosis occurs in 2% to 3% of ileal conduits. If a conduit is required after abdominal irradiation, use of a jejunal or proximal ileal segment or transverse colon conduit should be considered. Approximately 4% of patients with preoperative irradiation will develop fistulas when diverted [4]. Electrolyte disturbances occur uncommonly, and renal calculi form in about 10% of unmodified refluxing ileal conduits. The need for an external appliance and its discomfort and skin irritation plus expense is an annoyance with intrinsic psychological as well as medical consequences.

Despite these faults, many of which can exist for continent diversions, the ileal conduit is an established, proven diversion. Operative morbidity and mortality is low, and it is the method of choice in patients with a short life expectancy.

Large-bowel diversion

The use of transverse colon or sigmoid colon for conduit diversion has the advantage of facilitating creation of an antireflux mechanism, and the lower incidence of pyelonephritis (8% to 13%) associated with such conduits may be due to this modification [14, 15]. In the case of extensive pelvic irradiation, which will spare the transverse colon, this conduit may be preferable to ileum [14, 16, 17]. Some report a higher incidence of stomal stenosis (10% to 60%) [11], although others dispute this and there is a tendency to prolapse (4%)

[18]. The transverse colon is particularly useful for high ureteral or renal pelvis diversion if the ureter is extensively diseased by tumor, fibrosis, or radiation.

Continent abdominal stoma

The first report of a urinary diversion to a continent abdominal stoma was by Gilchrist and Merricks in 1950 [19], which developed from an anecdotal report of a cecal pouch reservoir with the appendix as a conduit performed in South America in the 1940s. Between 1949 and 1963, they performed 40 ileocecal-ascending colon segment urinary diversions, with a 15% mortality and a 94% reported continence rate. However, other surgeons were unable to reproduce their results, as the efferent unmodified ileocecal valve could not predictably produce continence in the majority of patients. A resurgance of interest followed the successful development of the Kock continent ileostomy for patients undergoing proctocolectomy for ulcerative colitis [20]. In the original procedure, there was no special valvular mechanism and continence depended on low pressure within the pouch and the constricting action of the rectus muscles around the ileum. Continence was unpredictable, so the concept of a nipple valve was introduced based on an old surgical technique originally described by Watsudji in 1899 in the formation of gastrostomies [21].

The Kock pouch

The idea of an ileal pouch with a continent nipple as inspired by Kock was first applied to the urinary tract by Leisinger in 1976 [22]. His successful clinical experience was followed by reports by Madegan [23], Kock and associates [24, 25], Ashken [26], Gerber [27], and, more recently, a large series by Skinner and associates [28–30]. Initially, the procedure was beset by a high incidence of problems, mostly related to the efferent nipple, which had a propensity to evaginate, with resultant incontinence, or to become difficult to catheterize. In 1980, Kock described an improved technique for its construction, advocating that the 5 cm long ileal intussusception be secured by four rows of intestinal staples [31]. Further stability was added by the use of a fascial or Marlex mesh collar around the base of the ileum where it exited from the intussusception. The collar fixed the pouch and intussusception securely to the anterior abdominal wall fascia, and, in addition to stabilizing the nipple, it improved the catheterizability by reducing redundancy between the abdominal wall and this intussusception. Because the mesentery contained within the intussusception was predisposed to evagination, Gerber suggested defatting the mesentery of the intussuscepted portion of the ileum [27]. Skinner and associates elaborated on this further by stripping 7–8 cm of mesentery off the ileum at the site of intussusception so as to totally exclude

it, this based on a description originally by Hendren to retain intussusceptions of the ileocecal valve in undiversions [32].

Improved nipple valve stability is ensured by attaching the nipple to the side wall of the reservoir by one row of staples so that a continuously increasing centripetal force works against the natural extrusion force, which would occur were the attachments not present (Fig. 1). Kock has shown that staples become embedded in the muscular layer of the nipple, completely covered by regenerating mucosa. Only the three staples at the tip of the intussusception are unlikely to become covered and thus should be routinely removed. Should stones form, they are easily removed from the reservoir endoscopically.

Bacterial colonization of the urine is common in all catheterizable urinary reservoirs, but pyelonephritis is generally rare, providing an adequate antireflux mechanism is created. Similarly, absorption through the reservoir is not usually a long-term problem, perhaps because the ileal mucosa adapts over time by a reduction in villous height, culminating in a nearly flat mucosa with decreased absorptive surface area, and only those with impaired renal function are likely to develop hyperchloremic acidosis.

The Kock pouch procedure continues to be modified, and the technique described here demonstrates the current state of the art. Aided by these modifications, the revision rate for stomas has been reduced from a high of 58% in the original series of Kock to a current low of around 10% in most reported series [27, 30]. It requires meticulous attention to detail, particularly

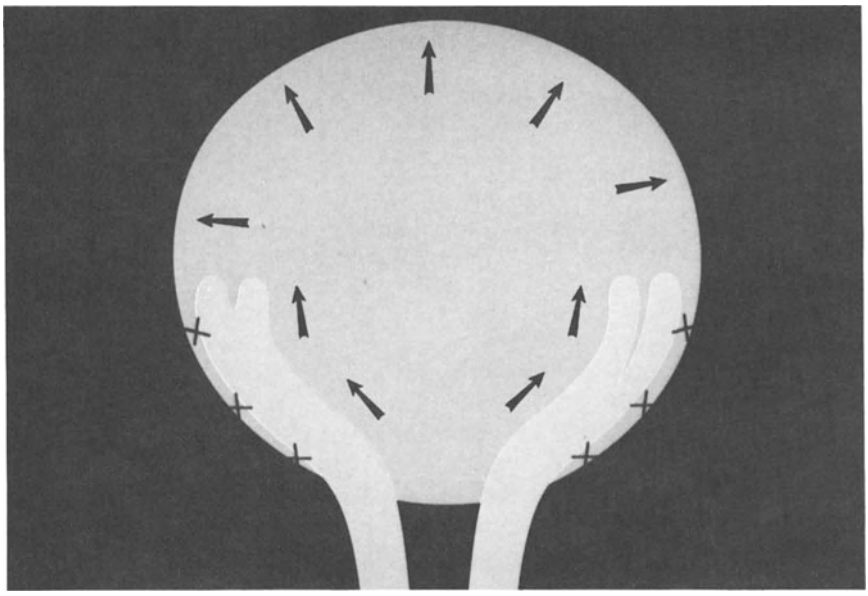

Figure 1. Improved nipple valve stability is ensured by attaching the nipple to the side wall of the reservoir so that increasing centripetal force increases valve competence.

with respect to the formation of the nipple valves on which the entire success of continence, catheterizability, and prevention of reflux relies. Due to the high learning curve with this procedure, it is not a procedure for the occasional surgeon. Despite suggestions that its performance requires only 1–2 more hours of operating time than the standard ileal conduit, many surgeons find it to be an arduous operation, and many will prefer a 'two-team' approach when it is performed in conjunction with radical cystoprostatectomy.

Technical aspects of the Kock pouch are only briefly described, as details with current modifications are presented elsewhere [30, 33, 34]. A 70–80 cm length of ileum is isolated, and a 44 cm length at the midportion of the segment is opened along its antimesenteric border and ultimately remodeled to form the reservoir (Fig. 2). The antireflux and continence nipples are fashioned by intussusception of the afferent and efferent tubular segments of ileum. A 5–6 cm length nipple is intussuscepted after 8 cm of mesenteric

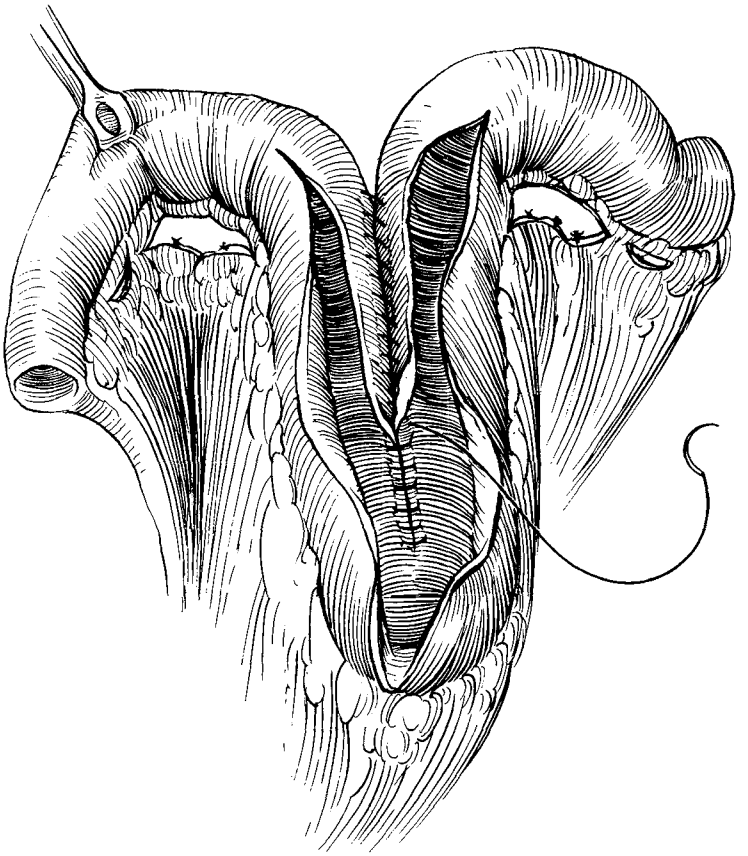

Figure 2. Remodeling a 70–80 cm length of ileum along its antimesenteric border to form a Kock pouch reservoir. (From Webster GD: Continent urinary diversion. Adv in Urol 1: 269, 1988.)

stripping. The nipple is secured by four rows of staples, three through the nipple alone and a fourth row securing the nipple to the reservoir wall (Fig. 3). A collar of Dexon mesh encircles the ileum as it enters the intussusception and is sutured so as to further promote nipple stability and to promote pouch fixation to the abdominal wall. The ureters are stented across the afferent nipple, and the pouch is drained for 3 weeks by a large-bore catheter through the continent nipple. The pouch is then activated by removal of stents and catheters after an excretory urogram and a Kock-o-gram confirm no obstruction or extravasation.

Early complications include those of anastomotic urine leakage from the reservoir or ureteroileal anastomoses, but these are minimized by careful stenting and drainage. Early nipple complications include necrosis or splitting along a staple line, generally ascribed to poor vascular supply and tearing, and manifesting later as reflux or leakage. Leakage can also be due to a short or hypomobile valve, from valve prolapse or valve fistula, which may form at the pin site on the staple line. Difficulty with catheterization can be caused by parastomal hernias or redundancy of the portion of ileum between the abdominal wall and the pouch itself. Late complications include pyelonephritis (1% to 2%), ureteroileal obstruction (3%), and late ureteral reflux (3%).

Despite the surgical difficulties and the incidence of postoperative prob-

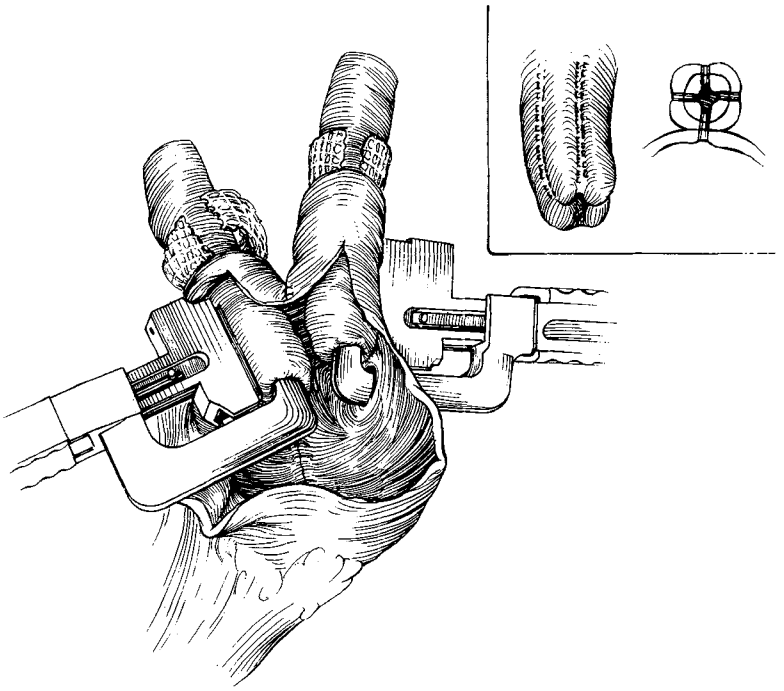

Figure 3. Staples secure the afferent and efferent valve mechanism to the reservoir wall for increased stability. (From Webster GD: Continent urinary diversion. Adv in Urol 1: 269, 1988.)

lems, most surgeons performing the procedure are enthusiastic, and most patients, even those who have needed one or two revisions, would not trade for an appliance-based ostomy. Hospitalization time has been reported as 50% greater than a standard ileal conduit [35]. Skinner reviewed his results in 1988, in 531 patients with Kock pouches, 378 of which were performed in conjunction with radical cystectomy [3]. Perioperative mortality was 1.9%, and operative complications were 16%, although they were higher before technical expertise was acquired. Eighty-seven of 489 patients (18%) with Kock pouches and cutaneous stomas had urine leakage for any reason. Patient acceptance of the procedure was high, with a 1.5% incidence of conversion to an ileal conduit [36], improved self image, and more physical and social interactions [37] reported.

The Kock pouch continues to undergo modifications to improve its reliability and to simplify the surgical technique. One of these includes elimination of the afferent nipple by implantation of the ureters into the afferent limb by either a Camey or split-cuff nipple technique, which are both reliable and considerably shorten operative time [38].

Continent ileocecal reservoirs

The major criticism of the Kock pouch is that it is a complex, time-consuming operation; however, all recognize its advantages as a capacious low-pressure reservoir with superior bowel dynamics and few or absent phasic contractions. Based on the original work by Gilchrist and because of the simplicity of construction of a right colon reservoir, others continue to improve this procedure by either modifying the ileocecal intussusception to enhance its continence or by colon detubularization or patching with adjacent small bowel to improve reservoir pressure characteristics [39].

The Gilchrist ileocecal reservoir

In 1950, Gilchrist described dog investigations and a human trial of an unmodified ileocecal reservoir using slightly over half of the proximal right colon, tunneled reimplants of the ureters into cecum, and a catheterizable ileocutaneous stoma (Fig. 4) [39]. He later described 40 patients, reporting a 94% complete continence rate with catheterization every 4–6 hours and nightly catheterization, 7% ureteral reflux, 6% reservoir calculi formation, and 4% pyelonephritis [40].

The Ashken reservoir

The ileocecal valve problem was extensively modified by Ashken in an attempt to improve continence reliability [41]. He initially used an isolated ileocecal segment with the ureters anastomosed to the terminal ileum, protected from reflux by the unmodified ileocecal valve. A separate 5 cm length

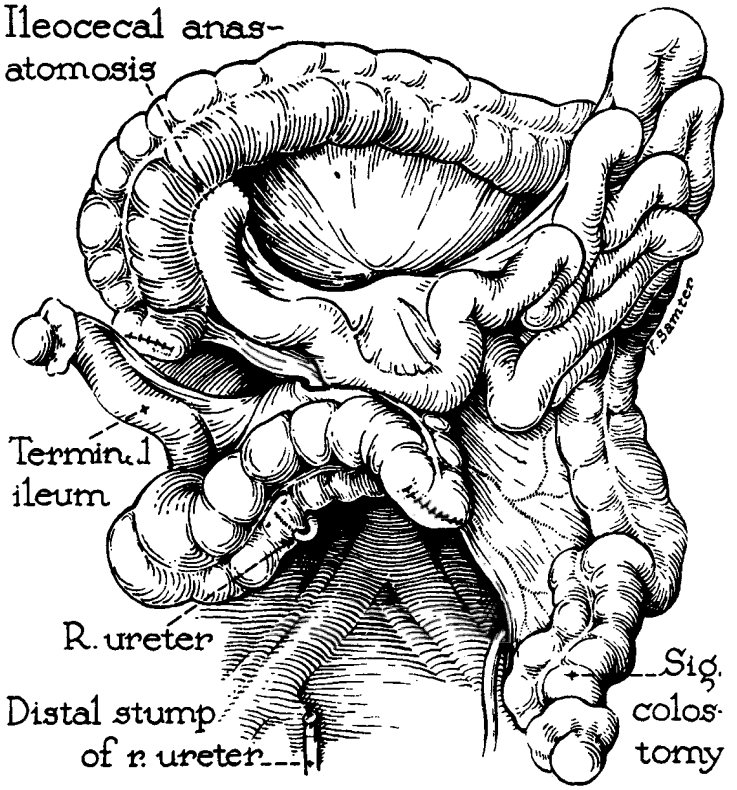

Figure 4. The Gilchrist unmodified ileocecal reservoir described in 1950, with a catheterizable ileocutaneous stoma. (From Gilchrist RK, Merricks JW, Hamlin HH, Rieger LT: Construction of a substitute bladder and urethra. Surg Gyn Obstet 90: 755, 1950.)

of ileum was sutured into the open end of the cecum to act as a continence mechanism (Fig. 5). However, the method failed, with prolapse of the ileocecal spout valve occurring in three out of seven patients. A modification in which the ileal spout valve was brought through the true ileocecal sphincter similarly failed, as did an ileal spout system fashioned as a flutter valve sewn into the open end of the cecum [42, 43].

Intussusception of the ileocecal valve into cecum

In 1977, a continent cecal reservoir using sutured intussusception of 12 cm of terminal ileum through the ileocecal valve to form a nipple into isolated cecum was described by Zingg and Tscholl (Fig. 6) [44]. Two of three patients were continent, although devagination of the intussusception at the mesenteric border similar to that which occurred in the earlier experience of Kock and associates was reported to be a recurrent problem.

Mansson studied a variety of methods to stabilize the intussuscepted

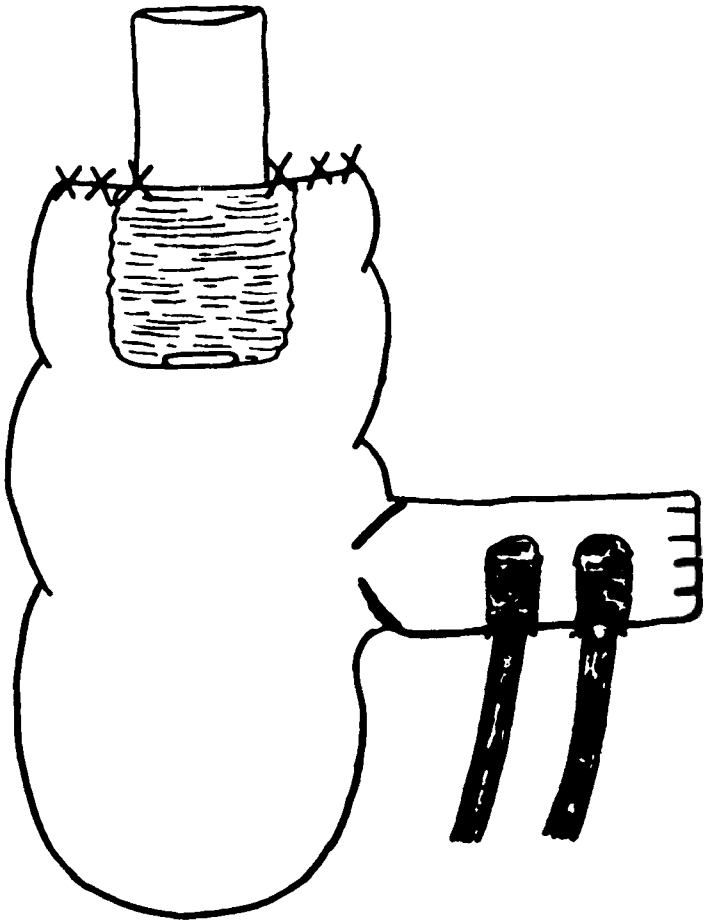

Figure 5. The Ashken reservoir using an unmodified ileocecal valve to prevent reflux and a seperate length of ileum for continence. (From Ashken MH: An appliance-free ileocecal urinary diversion: Preliminary communication. Br J Urol 46: 633, 1974.)

ileocecal valve [45–48]. His final modification uses a 5 cm intussusception of the ileocecal valve with mesenteric exclusion to debulk the intussusception, intestinal staples of the nipple valve, and a circumferential rectus fascial strip at the nipple base to stabilize the efferent limb to the skin for catheterization.

This is similar to the procedure described by Webster and Bertram [49] using the complete right colon and split-cuff nipple reimplantation into cecum to prevent reflux. Intussuscepted ileocecal nipple stability was produced by mesenteric occlusion, deep seromuscular coagulation of the intussuscepted serosa to promote fibrosis, three rows of intestinal staples, and a Marlex mesh collar of the efferent limb (Fig. 7). Using this technique, the hyperactivity within the nondetubularized right colon segment led to incontinence in three of seven cases, controlled by anticholinergic medication.

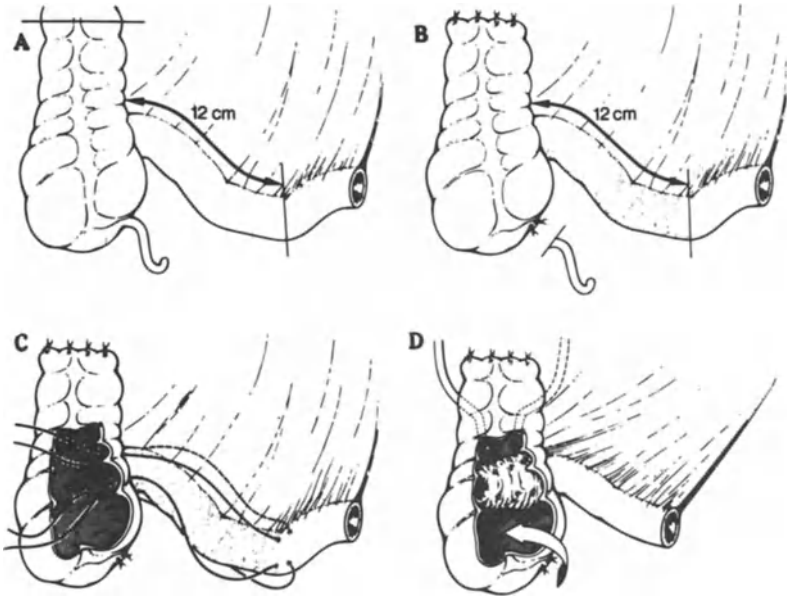

Figure 6. Intussusception of terminal ileum through the ileocecal valve to form an efferent continence mechanism in a cecal reservoir. (From Zingg E, Tscholl R: Continent cecoileal conduit, preliminary report. J Urol 118: 725, 1977.)

With further experience, the original technique has been modified so that the ileocecal intussusception is performed in an identical fashion with the ileocecal intussusception in a Kock pouch, as reported by Skinner (Fig. 8). The entire length of the right colon segment is detubularized and folded on itself to create a pouch, significantly modifying the hyperactivity normally seen in the nondetubularized segments and resolving the problem of spurting incontinence (Fig. 9) [49–50]. King and associates [51], attempting to avoid the use of staples, stabilized the intussusception by suturing the intussuscepted nipple to the reservoir wall, using muscle-to-muscle bonds (Fig. 10).

Benchekroun reservoir

Benchekroun has devised a continent urinary reservoir fashioned from 15 cm of nondetubularized right colon with its attached terminal ileum. The ureters were implanted into the terminal ileum with the unmodified ileocecal valve to prevent reflux, as described by Ashken, and a separate 14 cm segment of ileum or a separate vascular pedicle was isolated and intussuscepted upon itself so that the mucosal surfaces were opposed and the serosa surfaces formed luminal and external surfaces (Fig. 11) [52, 53]. Its construction allows urine from the pouch to enter between the epithelialized leaves of the intussusception to provide compression along the whole length of the continence mechanism. However, evagination has occurred in 18 of 62 cases,

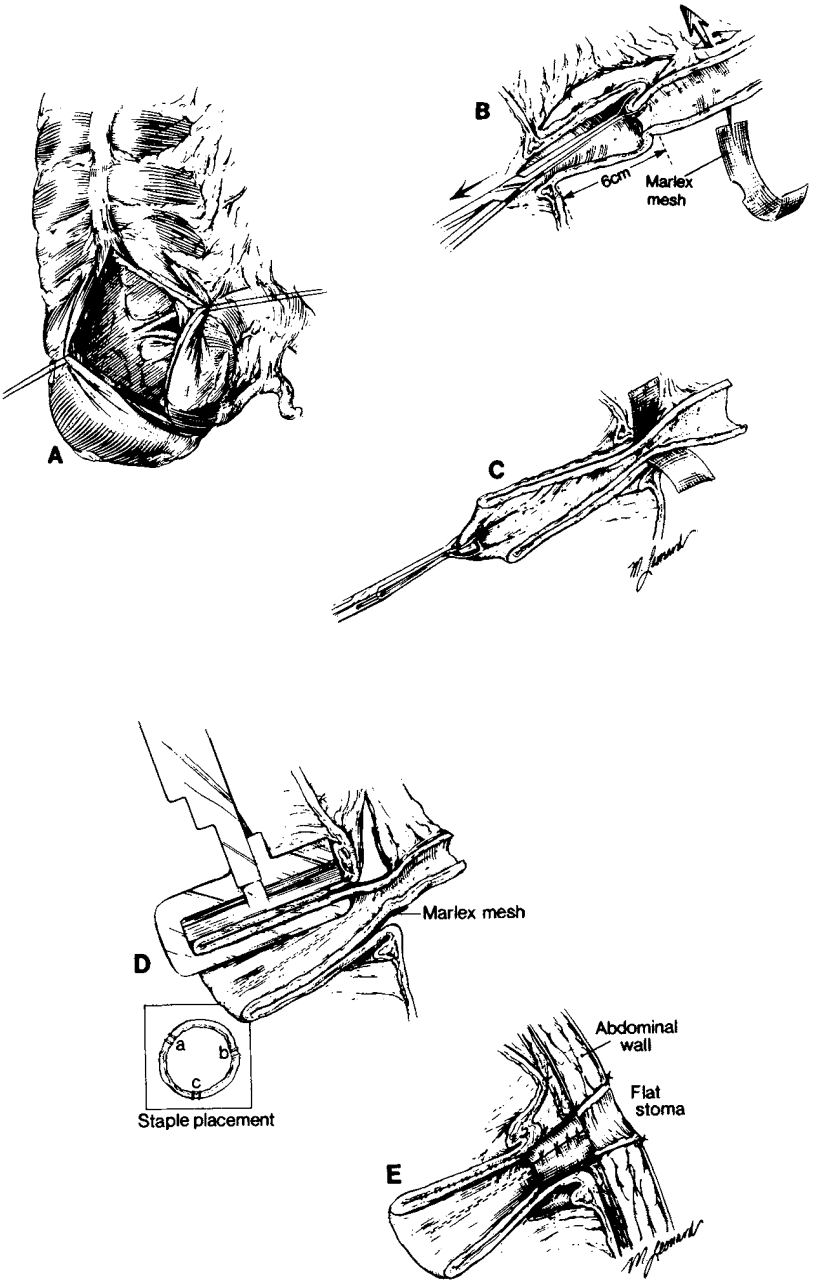

Figure 7. Mesenteric occlusion, seromuscular coagulation, staples, and a Marlex collar stabilize the intussuscepted ileocecal nipple. (From Webster GD, Bertram RA: Continent catheterizable urinary diversion using the ileocecal segment with stapled intussusception of the ileocecal valve. J Urol 135: 467, 1986.)

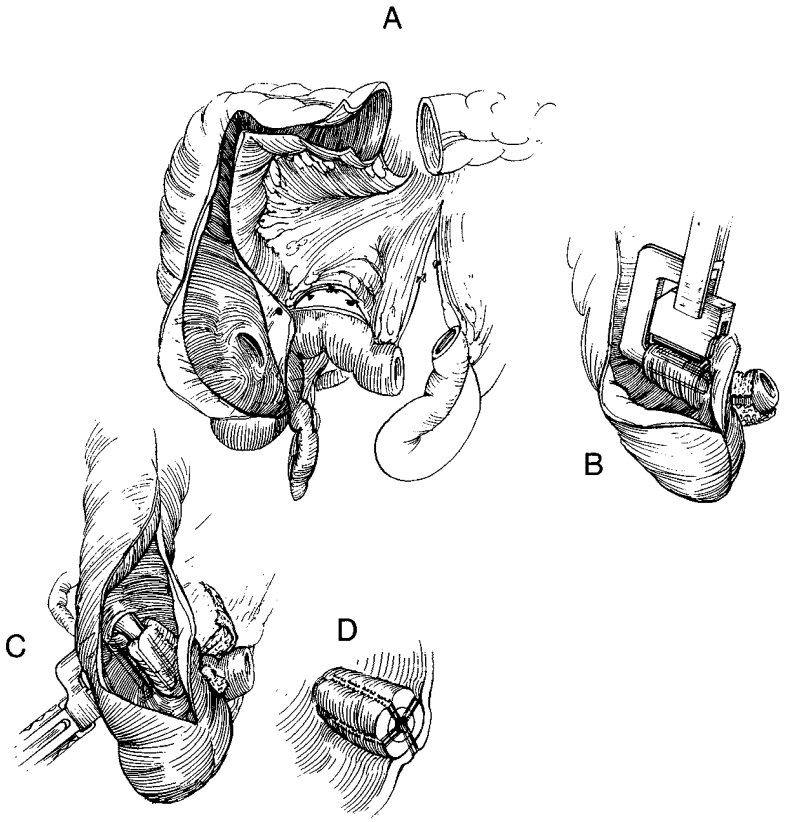

Figure 8. Illeocecal intussusception and stapling of the efferent nipple in a cecal reservoir. (From Webster GD: Continent urinary diversion. Adv in Urol 1: 269, 1988.)

but after revision, 58 of 62 patients are continent. High cecal reservoir pressure in the nondetubularized segment was a problem that improved 3 months postoperatively and was perceived only at filling above 500 ml.

Mainz pouch

Thuroff reported construction of an ileocecal pouch from an open segment of right colon, cecum, and adjacent ileum (mixed augmentation ileum n'zecum, Mainz pouch) for continent diversion [54, 55]. The pouch so created can be brought to the abdominal wall as a catheterizable stoma, relying on an ileoileal intussusception (Fig. 12), or to the native urethra, with a prosthetic sphincter for continence. The object of detubularization and patching of the right colon with small intestine was to ablate colonic hyperactivity, and they were moderately successful. Urodynamics studies 2 months postoperatively revealed a mean phasic contractile activity pressure of 63 cm of water, with a mean basal reservoir pressure of 39 cm of water at maximum capacity. An

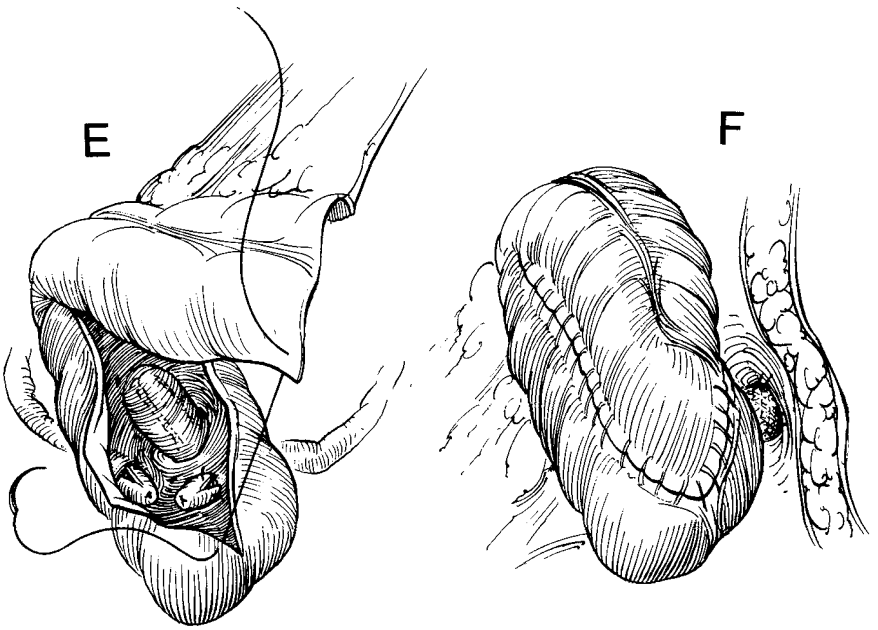

Figure 9. Detubularization of the right colon segment to reduce the hyperactivity and decrease the problem of spurting incontinence. (From Webster GD: Continent urinary diversion. Adv in Urol 1: 269, 1988.)

antireflux ureterocolonic anastomosis was employed. Six of 12 patients with ileoileal intussusception valve stoma were completely continent, as were an additional three of four patients with a stomal artificial sphincter.

The Mitrofanoff principle

Use of the appendix or an available isolated segment of ureter between the cecal urinary reservoir and the skin was described by Mitrofanoff [56] and further reported by Duckett in the pediatric literature (Fig. 13) [57]. The catheterizable conduit is narrow and implanted as a submucosal, tunneled nonrefluxing reimplant into the cecal reservoir, as are the afferent ureters. Though a 3–4 cm tunnel was used to prevent reflux, this mechanism failed in 3 of 24 patients. Nonetheless, this is a versatile and seemingly simple procedure to be considered in the reconstructive armamentarium.

The Indiana pouch

Rowland developed a partially detubularized right colon segment patched with a detubularized section of ileum, and relying for continence on the novel technique of plicating the terminal 10 cm of ileum just proximal to the ileocecal valve (Fig. 14) [58]. Once the pouch is created and the ureters

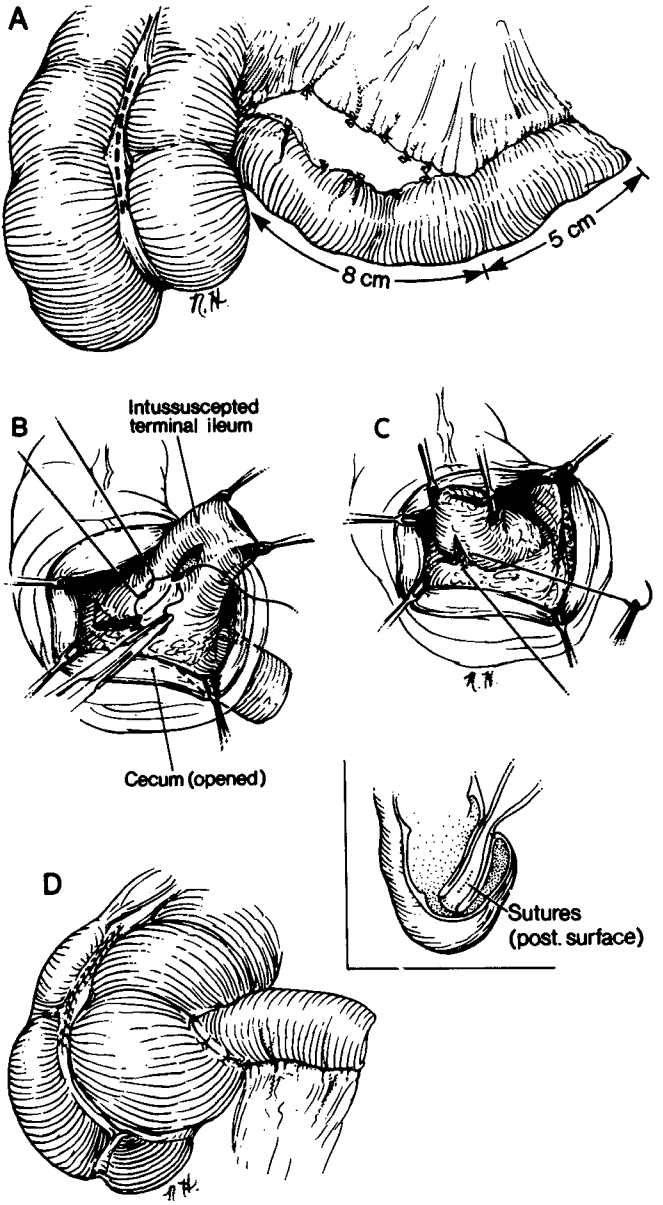

Figure 10. Avoiding staples and potential stone formation in the intussuscepted ileocecal valve using muscle-to-muscle bonds and dissolvable sutures. (From King LR, Robertson CN, Bertram RA: A new technique for the prevention of reflux in those undergoing bladder substitution or undiversion using bowel segments. World J Urol 3: 194, 1985.)

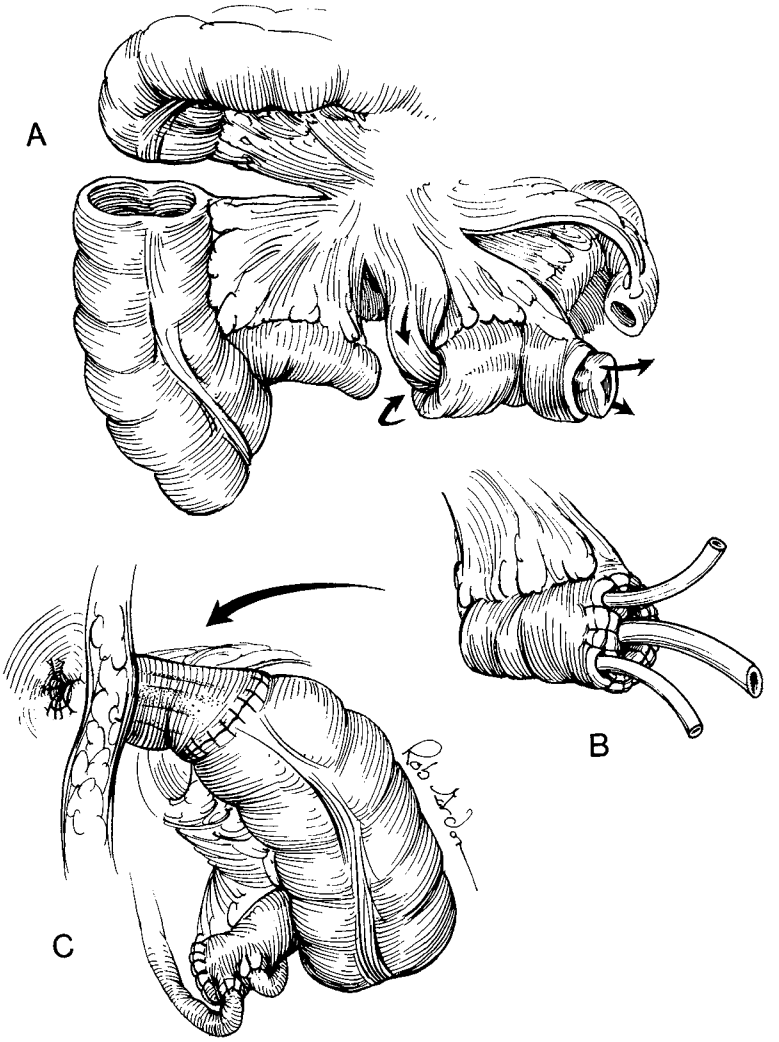

Figure 11. Continence provided by a separate ileal segment intussuscepted upon itself resulting in serosa forming luminal and external surfaces. (From Webster GD: Continent urinary diversion. Adv in Urol 1: 269, 1988.)

reimplanted by tunneled ureteral implantations along the tinea of the cecum [59], a 14 French rubber catheter is passed through the terminal ileum into the pouch and acts as a stent, over which a two-layer plication is performed from the ileocecal valve to the free end of the ileal segment. Though the 14 French catheter is held snuggly within the sphincterlike reduced lumen of the ileum, the segment is still catheterizable using an 18 or 20 French catheter. The stoma is usually brought out through the rectus muscle, and a flush stoma is created on the abdominal wall. The flexibility of this procedure is that the

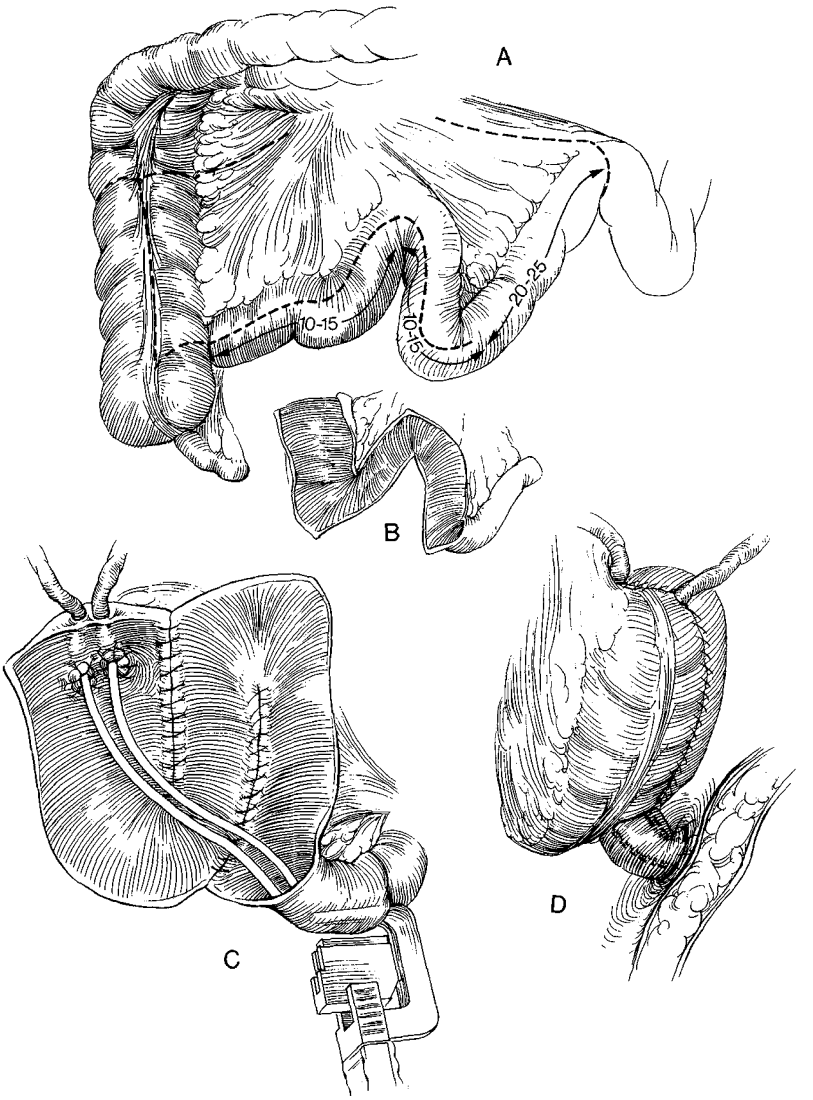

Figure 12. The Mainz pouch can be brought to the abdominal wall as a catheterizable stoma relying on ileoileal intussusception. (From Webster GD: Continent urinary diversion. Adv in Urol 1: 269, 1988.)

plicated ileal segment can be adapted for intermittent orthotopic catheterization. The initial volume of the Indiana pouch (500 ml) is greater than the Kock pouch if 25–30 cm of right colon is used, but, despite detubularization, intraluminal reservoir pressures are greater as well. Sigmoid colon can alternatively be used. Proponents of this diversion maintain that it is simpler to perform than a Kock pouch and no staples are in contact with urine, reducing the risk of stone formation. However, a 28% complication rate has

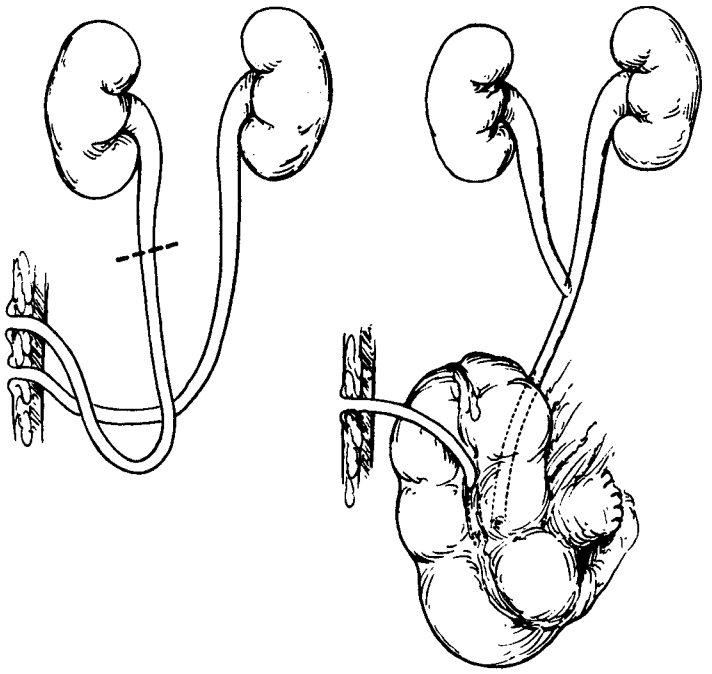

Figure 13. The Mitrofanoff principle using appendix or available isolated ureter for catheterizable continence. (From Duckett JW, McSnyder H: Use of the Mitrofanoff principle in urinary reconstruction. World J Urol 3: 191, 1985.)

been reported, including 8% major incontinence and 6% pyelonephritis, with a 13% reoperation rate [14]. Ninety-three percent of patients report acceptable daytime continence, 50% of patients are dry with once-nightly catheterization, 22% of patients are dry at night without catheterization, and 22% refuse awakening for catheterization and are incontinent at night [60].

Gastric reservoirs

Theoretically, stomach urinary reservoirs have the advantage of being practically nonabsorbing, with a minimal electrolyte loss and gastric acid inhibition of bacterial growth [61]. Though reportedly able to mobilize gastric segments into the lower abdomen, the risk to the kidneys of failure of the antireflux mechanism and patient morbidity of gastric complications to a major operative procedure makes most reconstructive urologists reluctant to construct gastric reservoirs.

Orthotopic bladder replacement

In-situ procedures seem to be the ultimate continent urinary diversion, as they preserve voiding through the natural pathway. Couvelaire in 1951

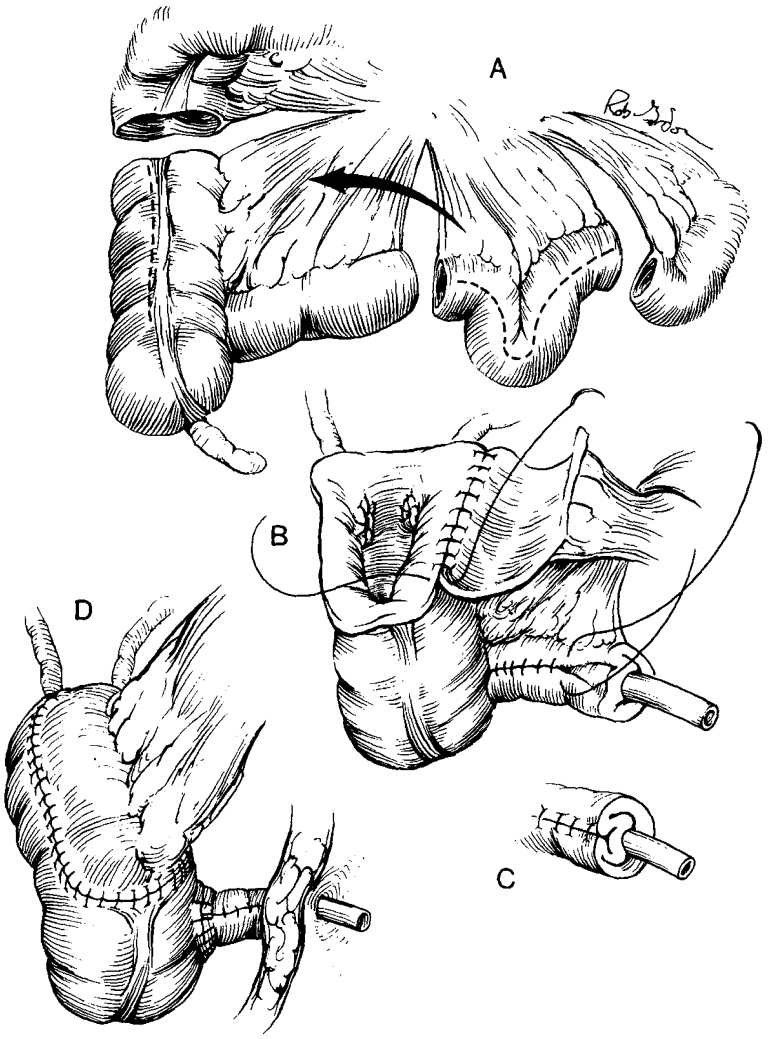

Figure 14. The Indiana pouch relies on plication of the terminal ileum for continence and reduces contractions by detubularization or an ileal patch. (From Webster GD: Continent urinary diversion. Adv in Urol 1: 269, 1988.)

reported the first attempt to anastomose an ileal segment to the urethra for bladder replacement [62]. In 1958, Camey elaborated on this procedure and reported on 185 patients in 1987 [63]. During this period, ileocecal and sigmoid segments were also reported to have been successfully used for bladder replacement by Kerr [64], Deleveliotis and Macris [65], Gil-Vernet [66], and Turner-Warwick and Ashken [67]. Hradec compared the use of various unmodified bowel segments for bladder replacement in 114 patients and concluded that ileocolonic or sigmoid segments were superior to small bowel [68]. Khafagy subsequently described the use of ileocecal segments for

bladder replacement, with the ureters anastomosed to the ileum and the cecum anastomosed to the prostatic urethra of males or the bladder neck of females [69]. Although all patients were continent by day, many had nocturnal enuresis, particularly if the bladder neck had been incompletely preserved. This operation met criticism for failing to achieve the goals of cancer surgery because of preservation of part of the prostatic urethra or bladder neck.

There is currently no consensus regarding an optimal orthotopic procedure and the procedures continue to evolve. Recent developments, including an appreciation of the importance of bowel detubularization and remodeling, and the use of the artificial urinary sphincter, have offered us further alternatives, even in those patients with sphincter dysfunction [70, 71]. Patients are free of the expense and care of applicance-dependent ostomies and often of catheters as well. Sexual function can potentially be preserved, as some of the previously sacrificed nerve fibers may contribute to continence [72]. The majority of patients considered for orthotopic bladder replacement have undergone cystoprostatectomy for bladder carcinoma, and the potential for urethral tumor recurrence is a criticism of these procedures. In performing these operations, the urethra must be kept under careful surveillance, as transitional cell carcinoma has a 7% to 10% incidence of concurrent or subsequent urethral carcinoma [73]. In patients with diffuse in-situ carcinoma of the bladder, multifocal tumors, involvement of prostatic urethra, or particularly in those in which there is any suspicion of a positive urethral margin on frozen section at the time of surgery, orthotopic diversion is precluded. These procedures are inappropriate for women, as an adequate cancer operation in females requires urethrectomy. Extreme obesity is also a relative contraindication, though orthotopic placement may be preferable to efferent limb problems in such patients. Patients should understand that gaining control of the new bladder requires some perseverance and fortitude, and sometimes reoperation.

The Camey procedure

There is no doubt that Camey has led the way in orthotopic diversion. Over 30 years have elapsed since its first performance [63, 74]. Currently, a 40 cm segment of ileum is selected for mobility to allow the midpoint to be anastomosed to the membranous urethra without tension and to ensure that the segment is long enough to anastomose to the ureters above the iliac vessels (Fig. 15). Camey notes that in about 15% of cases the procedure is abandoned for an alternative due to inability to achieve a tension-free ileourethral anastomosis.

The ileourethral anastomosis is performed to a 1 cm hiatus on the antimesenteric border of the midpoint of the ileal segment, taking care to avoid injury to the musculature of the mebranous urethra by sutures. The ureters are implanted into their respective ileal ends by a Le Duc–Camey 3 cm deepithelialized furrow [75]. All anastomoses are stented for 14–16 days;

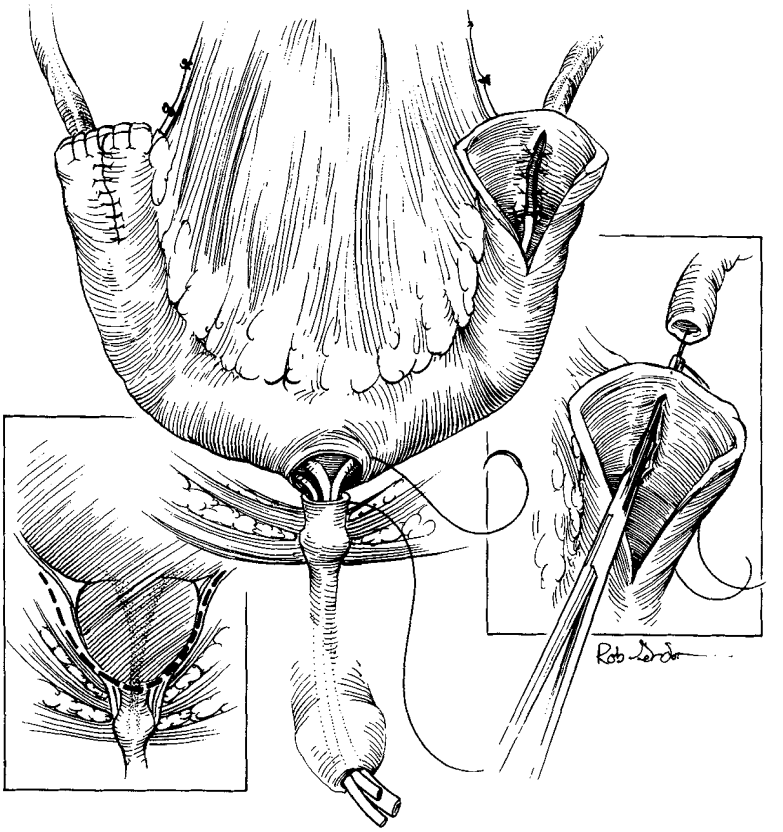

Figure 15. The Camey procedure for orthotopic diversion. (From Webster GD: Continent urinary diversion. Adv in Urol 1: 269, 1988.)

periodic irrigation prevents mucous plugging, and contrast radiograms exclude anastomotic leakage before catheter removal.

Camey emphasizes careful dissection of the prostatic apex to preserve the distal sphincter mechanism and preservation of the cavernous nerve to avoid erectile dysfunction. Continence and efficient voiding are the main aims of this procedure, and daytime continence was achieved in 95% of cases performed in the past 10 years, though only about 50% of patients have nighttime continence. Sagalowsky reported 80% daytime continence with 100% enuresis [76]. Others have reported even higher daytime incontinence, largely due to the high-pressure contractions in the tubular ileal reservoir. Camey notes peristaltic pressure waves range from 75 to 100 cm of water, but the baseline pressure or compliance of the system is good at its functional capacity. Daytime continence is likely to be partly volitional rather than passive, as a drop of urine forced into the sensitive membranous urethra by the peristaltic waves warns the patients of imminent leakage and induces a strong voluntary temporary external sphincter contraction until the pressure

wave passes. Enuresis is probably from a failure of this warning as well as overdistension, and pharmacologic ablation has been unsuccessful.

Voiding occurs by volitional relaxation of the distal sphincter mechanism and valsalva evacuation. Between 36% and 70% of patients may have sterile urine without prophylaxis. Though ureteral reflux has been seen in about 20% of cases, no stenosis or upper tract deterioration has occurred. An oncologically satisfactory 56% 5-year survival is reported, with no urethral tumor recurrence in the past 78 cases.

Camey's postoperative complications have declined to 31% over the years, and only one death has been reported since 1970, perhaps due to advances in intensive care, parenteral nutrition, and antibiotics.

The significant possibility of nocturnal enuresis has led others to create capacious, low-pressure, docile reservoirs, relying on bowel detubularization and remodeling techniques, often by patching together adjacent open bowel loops [58, 77, 78]. These procedures can be modified by tapering the bowel segment from the reservoir to the urethra or by a prosthetic sphincter to overcome an inefficient distal sphincter mechanism [58, 70].

Ileal neobladders

Melchior [79] and Hautmann [80] described orthotopic bladder replacement using modified ileal segments in 1988. In the former case, a 40 cm ileal segment is opened on its antimesenteric border, except for its 8 cm proximal segment, which is intussuscepted for an antireflux nipple for afferent limb ureteral implantation. The open ileal segment is then situated in a 'U' shape, anastomosed to the urethral remnant, and closed as a cylindrical detubularized reservoir (Fig. 16). Reservoir capacity averaged only 300 ml, requiring voiding originally every 2 hours, and then later every 3 hours, and by 6 months 95% of the patients had daytime continence, though only 40% had nighttime continence. Morbidity and mortality was similar to the ileal conduit [79]. Hautmann describes a larger ileal reservoir using a 70 cm ileal segment that is completely detubularized. A spherical pouch is fashioned in a 'W' or 'M' shape, anastomosed to the urethra, and ureters are sewn into the reservoir as tunneled implants. To reduce organized pouch contractions, the bowel is remodeled and closed as a sphere, rather than as a cylinder (Fig. 17). Initial results are encouraging, as reservoir capacity averages 387 ml, 8 of 11 patients being completely dry day and night, half with nocturia. Three of 11 patients have stress incontinence symptoms during the day.

The orthotopic Kock

Skinner describes using a modified Kock pouch as an orthotopic reservoir (Fig. 18) [3]. A Kock pouch is constructed with the same amount of bowel and the same afferent nipple. The reservoir is closed towards the most dependent position near the urethra. No efferent nipple is constructed;

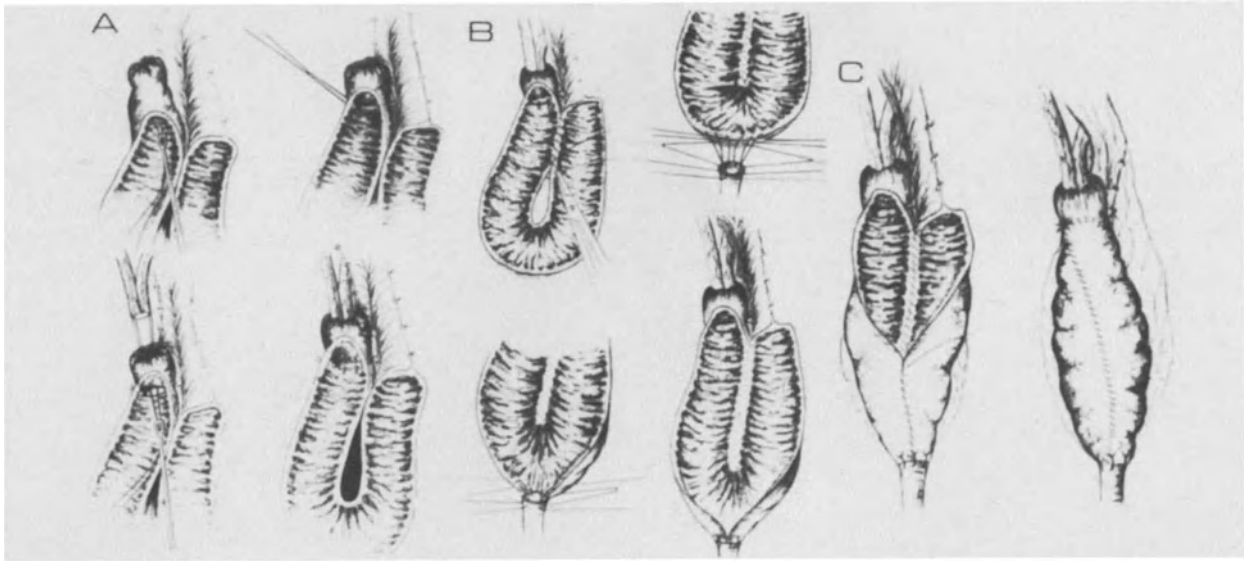

Figure 16. Detubularized ileal segment for orthotopic diversion. (From Melchior H, Spehr C, Knop-Wagenmann I, et al.: The continent ileal bladder for urinary tract reconstruction after cystectomy: A survey of 44 patients. J Urol 139: 715, 1988.)

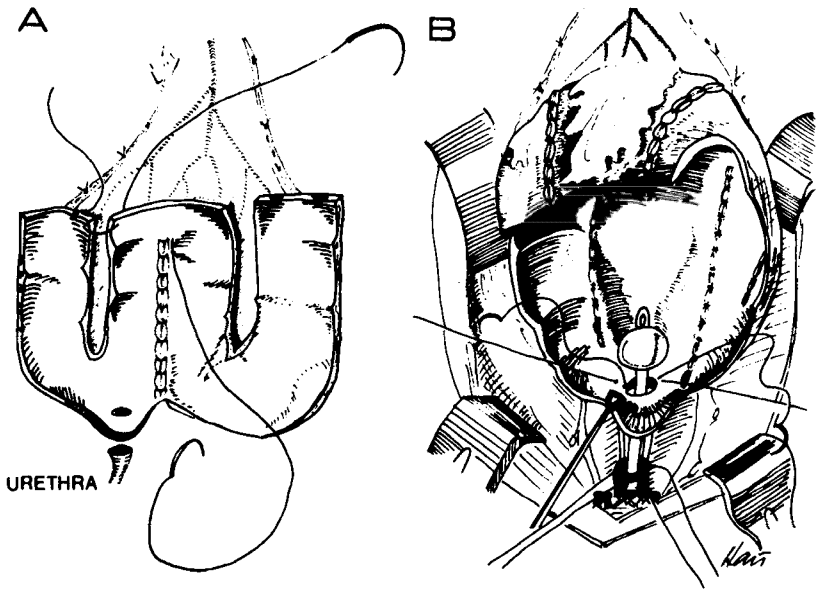

Figure 17. The spherical reservoir of the ileal neobladder. (From Hautmann RE, Egghart G, et al.: The ileal neobladder. J Urol 139: 40, 1988.)

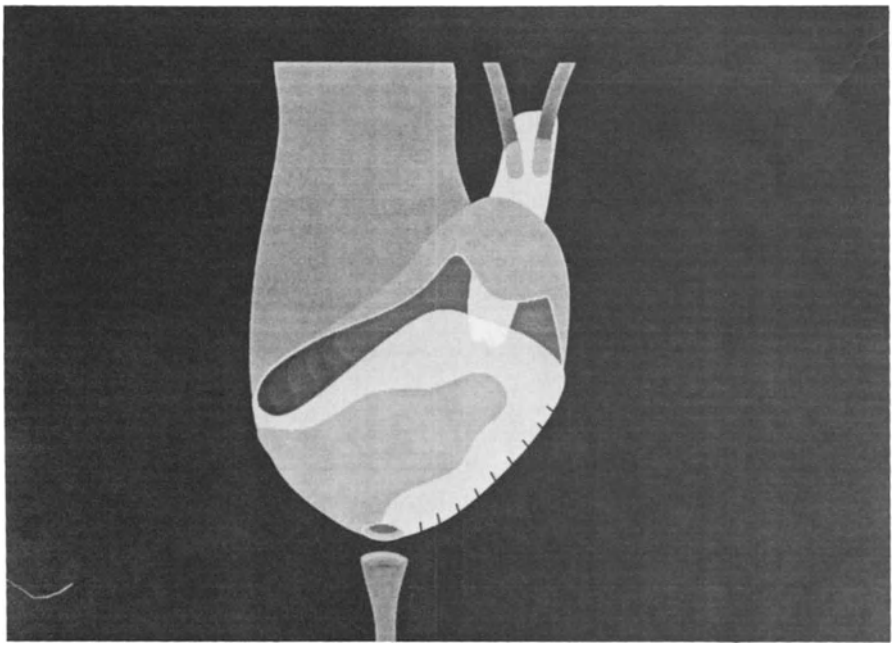

Figure 18. The modified Kock pouch as an orthotopic urinary reservoir.

rather, the dependent Kock opening is anastomosed directly to the urethra with approximately six dissolvable sutures. The urethral catheter is removed in 3 weeks if a cystogram and excretory urogram reveal no extravasation. Skinner's results parallel those of Melchior, with no daytime incontinence and 50% nighttime incontinence.

Detubularized and remodeled ileal orthotopic reservoirs have the lowest contraction pressures and the highest compliance of all current types of bowel reservoirs, and therefore may be physiologically superior to reservoirs using colon or ileocecal segments. Intrareservoir contraction pressures are generally less than 30 cm of water, usually low enough to avoid forcing urine through a urethral sphincter mechanism with 25–40 cm water resistance. Colon conduits average 30–40 cm of water contraction pressure and theoretically risk greater incontinence. Any detubularized bowel reservoir may still have contractions sufficient for leakage through a weak native urethral sphincter, in which case an artificial urinary sphincter can be employed.

Orthotopic ileocecal segments

Ileocecal segments have been used for orthotopic bladder replacement with very good results. Hradec [68] compared various unmodified bowel segments for bladder substitution in 114 patients, and, using urodynamics, he felt that ileocecal or sigmoid colon segments had greater capacity, more complete evacuation, and greater flow rates than ileal bladders. Although intrareservoir pressures are higher in colonic or ileocecal reservoirs and ileal reservoirs, even with Heineke-Mikulicz remodeling, the relative simplicity of construction had led to a variety of types of reservoir that differ in technique of remodeling, ureteral implantation, and antireflux mechanism. Each has its own advantages and disadvantages, and patient selection and urologist preference largely dictate choice.

Unmodified ileocecal segments

Gil-Vernet [66], Khafagy [81], and Alcini [82] reported their results with unremodeled ileocecal segments. In each case, ureters were implanted directly into the terminal ileum of the segment, and the unmodified ileocecal valve acted as the antireflux mechanism. The urethra was anastomosed directly to the cecum, with continence achieved by an intact external sphincter mechanism (Fig. 19). Gil-Vernet reported excellent results in 26 patients with good capacity, volitional voiding every 4–5 hours, satisfactory emptying, and a forceful stream [66]. He emphasized that the ileum between the cecum and ureters should be under no tension so as to preserve the antireflux geometry of Bauhin's valve and that cecostomy or appendicostomy should be used for defunctionalization during the healing phases.

Khafagy studied 130 of his patients with carcinoma of the bilharzial bladder [81]. He reported a 15% mortality, mostly due to sepsis, and five patients with

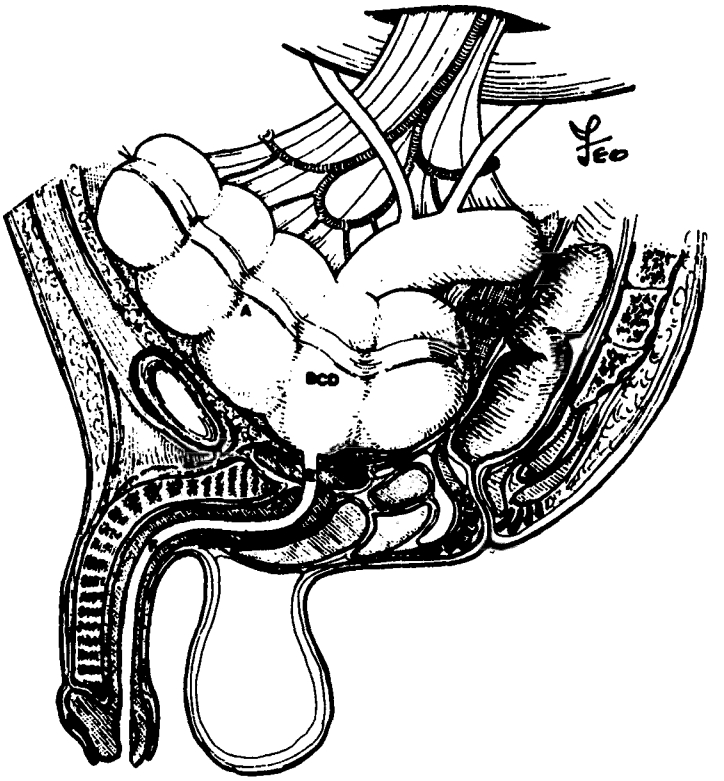

Figure 19. Unmodified ileocecal segment for orthotopic diversion, using unmodified ileocecal valve as the antireflux mechanism. (From Alcini E, D'Addessi A, Giustacchini M, et al.: Bladder reconstruction after cystectomy: Use of ileocecal segment and three-loop ileal reservoir. Urology 31: 10, 1988.)

fistulae. Though most patients had extreme urinary frequency early postoperatively, by 12 months 74% of patients voided every 2 hours or longer. Eight-two percent of patients reported daytime continence, though 76% of patients had nocturnal enuresis. Bladder capacity exceeded 350 ml and urodynamics demonstrated no vesicoureteral reflux in 10 of 10 patients studied, and all voided by abdominal straining.

Alcini reported similar technical aspects as other investigators in his 26 cases and further noted that his complications of pelvic abscesses and urinary fistulae might be due to preoperative radiation therapy, which has since been discontinued [82]. He reported that all his patients were continent by day, and all patients had nocturnal enuresis to varying degrees for 2 years postoperatively, which gradually diminished.

Zinman [83] similarly used a nondetubularized ileocecal segment anastomosed to the membranous urethra or apical prostatic capsule, and reinforced the ileocecal valve for reflux prevention to the ureters anastomosed into the ileal tail. However, in 3 of 14 men the reinforced ileocecal valve failed to

prevent reflux. Also, though the preservation of the apical prostatic capsular cuff aided the urethral anastomosis and facilitated potency sparing, the preservation of the apical prostatic cuff may potentially fail the goals of cancer surgery.

The orthotopic Indiana continent urinary diversion

After noting that poor continence occurred in half of patients when no attempt was made to disrupt the tubular configuration of the cecum due to poor compliance and mass contraction, Rowland detubularized the cecal reservoir, either by adding an ileal patch or sigmoid patch into the cecum or by fashioning a Heineke-Mikulicz reconfiguration [58, 59]. Adjacent open large and/or small intestinal plates are combined to form a pouch in further efforts to inhibit the mass contractions in the distended reservoir, which may lead to incontinence or reflux. However, fluoroscopic evaluation has shown that although spontaneous contractions are dampened or cancelled, they are not lost and are probably higher than ileal segments.

As currently described, 12 cm of terminal ileum and all 25–30 cm of right colon to the hepatic flexure are isolated, an appendectomy is peformed, and the colon is detubularized, except for a small cecal cap (Fig. 14). After plication of the terminal ileum and ureteral implantation into colonic tenia or the colon wall itself, the efferent limb is anastomosed to the male urethra or female perineum through the anterior vaginal wall (Fig. 20). This procedure is gaining popularity due to the initially high bladder capacity compared to ileal reservoirs, the relative ease of construction, absence of foreign bodies in contact with urine that leads to stone formation, adaptability of the technique to multiple stoma sites, and relative ease of reoperation. Rowland reports a 28% complication rate and a 13% reoperation rate, and most patients are dry day and night.

The orthotopic Mainz pouch and LeBag

The Mainz (mixed augmentation of ileum and cecum) pouch has been described in patients undergoing radical cystoprostatectomy. Constructed from 10–15 cm of proximal right colon and 15 cm of terminal ileum that has been remodeled in an 'N' configuration, the ureters are tunneled implantations into the cecum that prevent reflux and rely on the native external sphincter for continence. Rather than form an efferent intussuscepted ileal valve, an unmodified proximal ileal segment is anastomosed directly to the urethra. Thuroff [54, 55] noted that an artificial urinary sphincter positioned on the bulbar urethra or the efferent pouch limb may be needed to assist in urethral continence if the native urethral sphincter fails (Fig. 21).

Light and Engelman [77] described a similar procedure, however, all of the segment was detubularized, except only the two most proximal inches of ileum, which served as a site for the urethral anastomosis. This provides a

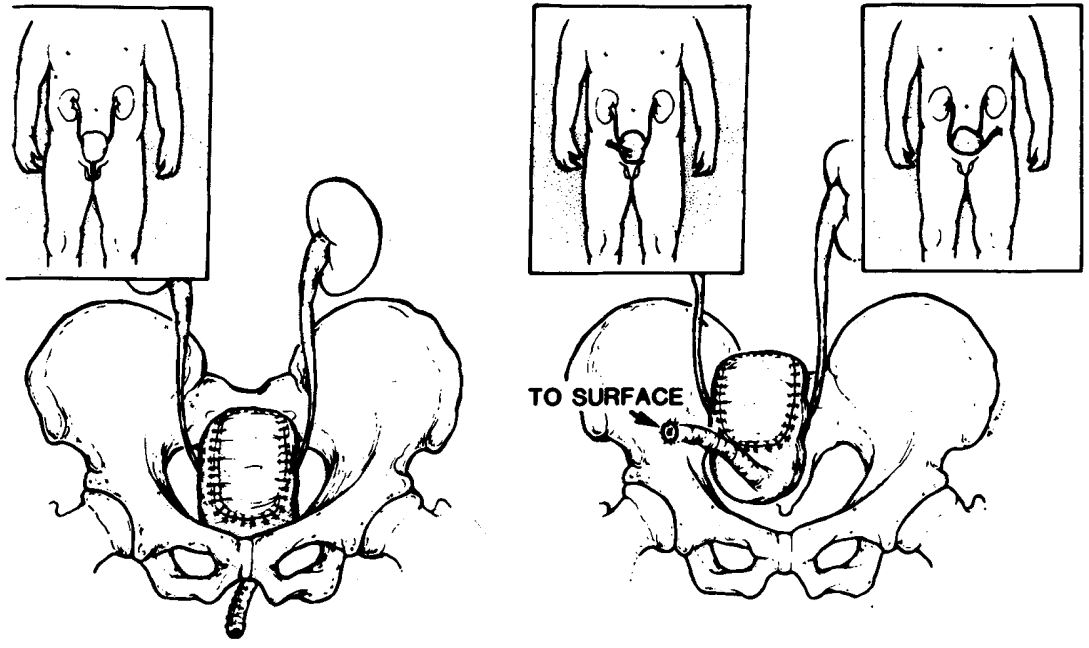

Figure 20. The Indiana pouch may be orthotopically anastomosed to the urethra or perineum, or brought to the surface as a catheterizable abdominal reservoir. (From Rowland RG, Mitchell ME, Bihrle R: The cecoileal continent urinary reservoir. World J Urol 3: 186, 1985.)

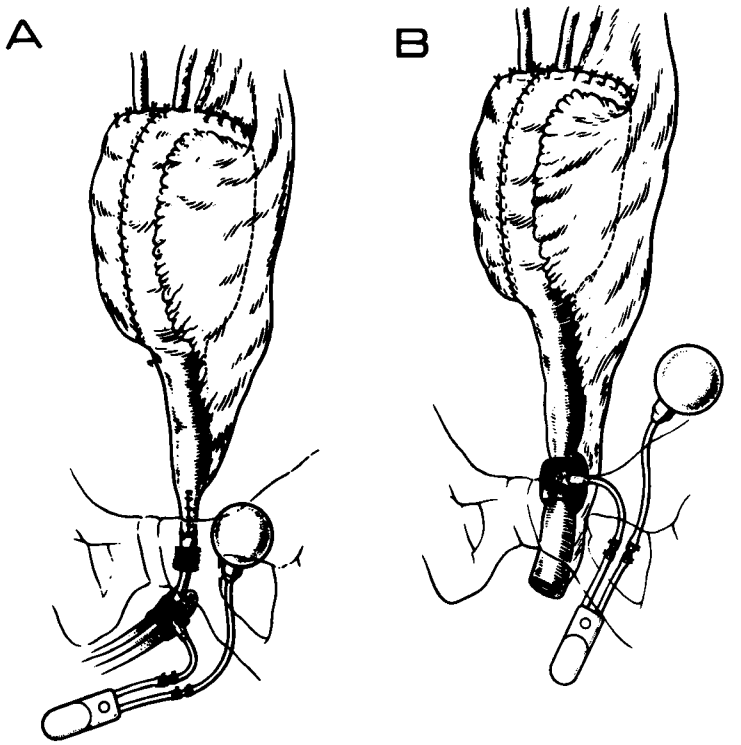

Figure 21. An artificial urinary sphincter may assist in urethral continence if the native urethral sphincter fails. Mainz pouch with (A) bulbar artificial urinary sphincter and (B) efferent pouch limb artificial sphincter. (From Thuroff JW, Alken T, Riedmiller H, et al.: The Mainz pouch (mixed augmentation, ileum and cecum) for bladder augmentation and continent diversion. J Urol 136: 26, 1986.)

stable orthotopic reservoir with 400–700 ml capacity. Resting pressure when full was between 20 and 45 cm of water, with low-amplitude contractions generally below 45 cm of water, so incontinence is possible without an additional artificial urinary sphincter.

Orthotopic colonic reservoirs

Camey and other groups [63, 65, 68] have reported that unmodified colon segments anastomosed to the urethra exhibit very-high-pressure contractions, which are propagated by the tubular-shaped bowel and lead to incontinence. For this reason, Goldwasser [78] modified these procedures by detubularizing the right colon segment. The entire right colon, including the proximal transverse colon as far as the middle colic vessels, provide a capacious storage reservoir, and the entire segment, except for the most dependent 8 cm of cecum, are detubularized and remodeled (Fig. 22). Ureters are implanted

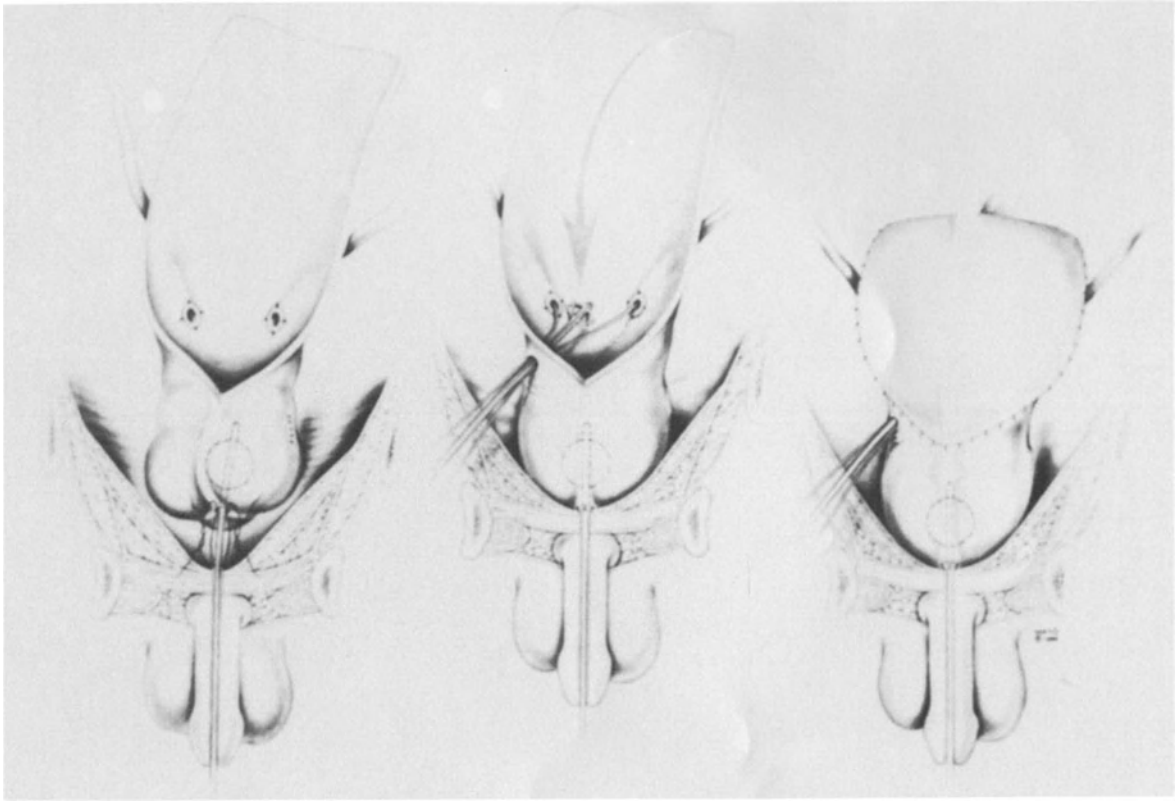

Figure 22. The detubularized right colon orthotopic reservoir with antireflux ureterocolic ananstomoses. (From Goldwasser B, Barrett DM, Benson C: Bladder replacement with use of a detubularized right colonic segment: Preliminary report of a new technique. Mayo Clinic Proc 61: 617, 1986.)

into the reservoir itself, and the dependent cecum is anastomosed to the membranous urethra.

Of seven patients, one was totally incontinent, presumably due to distal sphincter damage, but the other six patients voided every 3–6 hours day and night and experienced no incontinence. Reservoir capacity varied from 400 to 900 ml, with 20–35 ml residual urine, and voiding occurred by relaxation of the pelvic floor with abdominal valsalva.

Orthotopic reservoirs and the artificial urinary sphincter

The artificial urinary sphincter has achieved an established role in the management of intractable urinary incontinence, and it was natural for its role to be expanded to include orthotopic and even abdominal wall reservoirs. The device can be implanted around the intestinal neourethra if bulbar urethra is not available (Fig. 21) [70, 71]. Light and Scott noted sporadic diurnal incontinence with noctural enuresis in two of two patients with a device implanted around the tapered intestinal efferent limb of a nondetubularized sigmoid segment, although a third patient with a low-pressure ileocecal segment was dry [45]. Zinman used a prosthetic sphincter placed as a second stage or a urethral suspension 3–6 months after ureteroileocecourethroplasty for those 40% of patients who failed to achieve socially acceptable continence with his procedure [84]. The artifical sphincter, which is certainly less desirable than use of the native sphincter mechanism, expands the scope of orthotopic bladder replacement.

Complications such as erosion and infection of the device can be reduced by extreme care in implantation, but the incidence of revision surgery is high. Also, increasing artificial sphincter pressures that are too high to avoid incontinence create risks that subject the upper tracts to renal deterioration secondary to higher intrareservoir pressures, or eventual to failure of the antireflux mechanism [71].

Continent urinary diversion with the anal sphincter

Although the first description of urinary diversion to the bowel was as early as 1852 [85], it was the development of tunneled ureteral implantation by Coffey in 1911 [86] that permitted broader usage of a seemingly safe and simple surgical procedure that was socially acceptable and generally comfortable to the patient. Most disillusionment was met as a result of lack of prevention of reflux, upper tract infections, and serious electrolyte imbalances affecting many patients with ureterosigmoidostomies. Even with the nonrefluxing mucosa-to-mucosa technique of Politano and Leadbetter, over half of the patients developed acute pyelonephritis, up to a third of the patients developed upper tract deterioration, and 33% to 81% of patients suffered metabolic acidosis and electrolyte imbalances [87–89]. However, ureterosig-

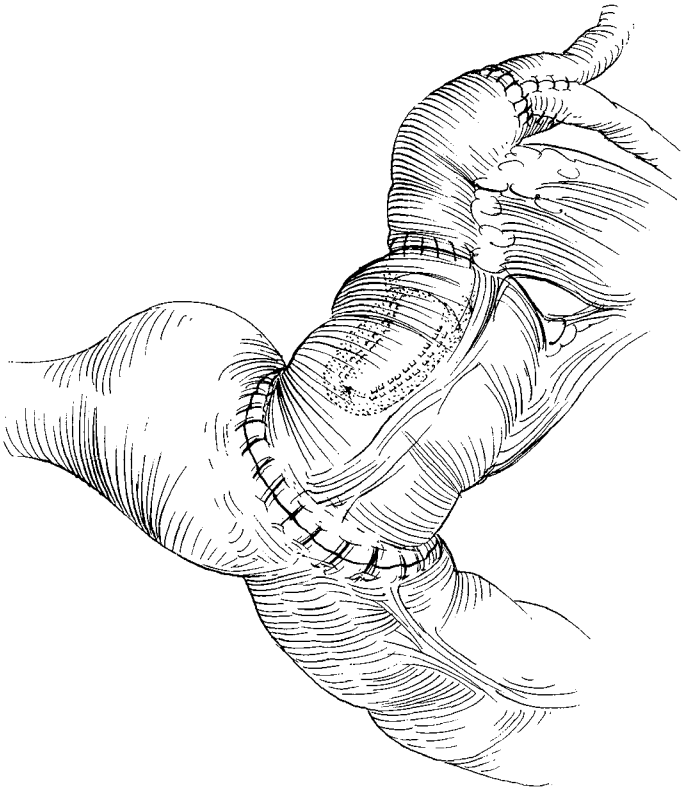

Figure 23. Ureteroileocecosigmoidostomies avoid a contaminated coloureteral anastomosis, provide an antireflux ileocecal valve, and use the rectal sphincter for continence. (From Webster GD: Continent urinary diversion. Adv in Urol 1: 269, 1988.)

moidostomy may have a place in the preterminal cancer patient who needs diversion when longevity is not a concern and care for a cutaneous ostomy would be difficult [4].

Seemingly, the final death knoll for ureterosigmoidostomy was the growing evidence of an increased rate of bowel adenocarcinomas at the anastomosis site, with 5% of those with ureterosigmoidostomies likely to develop tumors over a mean of 25 years [90]. This was believed to be due to urinary nitrate products converted by fecal bacteria to active carcinogenic nitrosomines, which act perferentially on intestinal cells. Neoplasia is rare in patients with ureteroileal conduits; one benign adenomatous polyp, one adenocarcinoid tumor, and one anaplastic tumor have been reported [91–93].

Ureteroileocecosigmoidostomies were an attempt to avoid a coloureteral anastomosis and to provide an antireflux ileocecal valve to protect the ureteroileal anastomosis from contact with feces (Fig. 23) [94]. Thus far, no tumors have been reported using this technique, but follow-up is not long. It is of some concern in this regard, however, as adenocarcinoma has been

reported arising in ureteroileocecocystoplasties [95]. Perhaps suture lines act as irritants that, in the presence of bacteria, form carcinogens.

Nonetheless, Kock has devised an AVR (*a*ugmented in *v*alve *r*ectum) [96]. An ileal patch is placed into the rectum, with a nipple valve formed using intussuscepted sigmoid. Ureters are implanted within the intussuscepted segment itself. Stool is temporarily diverted as a low cutaneous sigmoidostomy, then closed 2 months later after diversion healing has occurred. Alternatively, in the case of larger ureters that would not fit into a sigmoid intussusception, the sigmoid is left intact after placement of an ileal patch onto the rectum, and the ureters are implanted onto the butt end of an afferent ileal nipple, which is anastomosed into the rectum directly. Kock reports 700–900 ml capacity with low-pressures, daytime continence, and no nighttime enuresis, with emptying 0 to 2 times per night.

Skinner has modified Kock's AVR by placing a hemi-Kock pouch onto the sigmoid colon [3]. He noted higher volume capacity than the AVR with therefore more compliance and better urine control, and recommended it for patients without a urethra or at risk of urethral recurrence.

Conclusions

The field of continent urinary diversion has certainly not matured to the point where any one of these procedures can be considered best. Success relies on careful patient selection with particular regard to capabilities, expectations, and prognosis. Meticulous surgical technique is needed to achieve the goals of a low-pressure docile and capacious reservoir, a stable, functional continence mechanism, and prevention of reflux. Most of the aformentioned procedures can attain these goals, and often procedure selection depends on the individual surgeon's philosophy and past experiences, successes, and failures. Eventually a generally overall preferred technique may develop, but in the meantime, it is highly desirable that the operating surgeon be acquainted with features of each of these techniques in order to be versatile when intraoperative circumstances dictate a change in standard technique. The ultimate role of each of these techniques will be dependent on the results of long-term follow-up in large series with good scientific reporting. Nonetheless, continent diversion procedures have widespread application in improving the quality of life in patients undergoing cystectomy.

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7. Laser treatment of transitional cell cancer of the bladder and upper urinary tract

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The therapeutic potential of lasers in the treatment of urologic malignancies has been explored in recent years by a number of investigators. Much enthusiasm has accompanied the use of this new technology, and the results have often been reported in glowing terms, leading to enormous expansion of laser usage. This chapter will review the basic principles of laser technology and its use in the treatment of transitional cell cancer of the bladder and the upper urinary tract, as well as review its possible advantages and disadvantages in relation to conventional methods of treatment.

Laser physics

The word '*laser*' is an acronym for *l*ight *a*mplification by the *s*timulated *e*mission of *r*adiation. A laser is the light energy part of the electromagnetic wave spectrum.

In a normal population of atoms, the majority will be in a resting state, and a small percentage will be at a higher energy level. The addition of external energy from a pump source will induce spontaneous absorption of energy, that is, the atoms in the resting state will rise to higher energy levels. Thus, more atoms will be in the excited or high-energy state, resulting in an unstable situation known as a *population inversion*. Such unstable atoms tend to give off their extra packet of energy in the form of photons and to return to the resting state, a phenomenon known as *spontaneous emission*.

Regardless of what type of energy source was used to create the population inversion, when the atoms release their extra photons of energy, they do so at wavelength determined by the atoms involved. When spontaneous emission occurs, the released photons of energy strike other atoms in a high-energy state. Each target atom then gives off the striking photon and emits a second photon of light of the same wavelength as the atom returns to the resting state. Thus, in this process, known as *stimulated emission*, one incoming photon has been amplified to two ongoing photons. These two photons are emitted exactly in phase and travel inthe same direction. Each can stimulate another atom, perpetuating the reaction.

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In a laser, the atoms in which this activity takes place (the lasing medium) are placed in a cylinder closed at both ends by mirrors. Most of the energy escapes tangentially to the axis of the cylinder. However, a small percentage of the beam is trapped between the mirrors, thus building up the reaction as the photons are reflected back into the medium. The front mirror has a small central aperture through which the laser beam can be released. Although this beam is often spoken of as *laser light*, and may indeed be visible, it differs from ordinary light in three ways: it is monochromatic (all the waves are of the same length), collimated (the waves are parallel), and coherent (all the waves are in phase).

The laser beam can be released as a continuous wave (CW). In a CW medical laser, the surgeon, by using a foot pedal, releases the beam at a steady rate for as long as the foot pedal is depressed. The level of energy (watts) emitted is determined by the power setting of the machine. Alternatively, the laser beam can be released in the pulse mode, that is, in burst lasting for a limited period of time, as determined by the machine setting. This mode is also useful in medicine.

Four types of lasers are available for urologic use today. First, there is the carbon dioxide (CO_2) laser. Ninety-seven percent of the energy of the CO_2 laser is absorbed at the point of contact, with a tissue penetration of only 0.1 mm. To date, transmission of the CO_2 laser via fiberoptics has not been perfected for clinical use, and the beam must therefore be directed by a series of mirrors. The CO_2 laser has a wavelength in the far-infrared invisible region of the spectrum, at which point the optical absorption of water is at its maximum. Thus, the CO_2 laser does not penetrate water. For these reaseons, this laser is not operative for endoscopic urologic surgery, and its main urologic use is in the treatment of cutaneous lesions, i.e., condylomata acuminata.

Second, there is the argon (Ar) laser, which can be transmitted by fiberoptics and penetrates water well. However, available Ar lasers are incapable of generating greater than 5–15 watts of power. In addition, approximately 55% of the power is reflected back from the tissue, and its wavelength is in the blue-green portion of the spectrum, in which the hemoglobin absorption is at its maximum, so selective absorption by hemoglobin occurs in preference to absorption by surrounding tissues. Thus, the Ar laser is generally unsuitable for ablation of tumors. Nonetheless, it will be discussed later in this chapter, as it can be used in photodynamic therapy in the treatment of bladder cancer.

Third, there is the neodymium:yttrium-aluminum garnet (Nd:YAG) laser, which operates within the near-infrared invisible region of the spectrum. Approximately 40% of its energy is reflected back from the tissue. However, it is not absorbed preferentially by any pigment, nor is it absorbed by water. Further, Nd:YAG lasers available for medical use are capable of generating as much as 100–125 watts of power, although greater than 50 watts is rarely

necessary for urology. In addition, it penetrates 4.0 mm into tissue, and it can easily be transmitted by quartz fiber. These features make this laser the ideal choice for endoscopic surgery.

Fourth, there is the candela tunable-dye laser, which has produced good preliminary results in ureteroscopic lithotripsy. It is not applicable to tumor ablation.

The remainder of this chapter will deal with the Nd:YAG laser only, unless otherwise specified.

Tissue effects

All three of these lasers produce their effects primarily by thermal action. Permanent or visible damage to the tissue dose not occur if tissue is heated below 60°C. From 60 to 100°C protein denaturation occurs. The tissue will turn white and disintegrate approximately 4–7 days later. This is the temperature range in which the Nd:YAG laser works, and, thus, the therapeutic action of the Nd:YAG laser is primarily through coagulation (over 100°C, vaporization and carbonization occur. This is the temperature range in which the CO_2 and argon lasers work).

The tissue effects of the Nd:YAG laser depend on the physical conditions of the delivery fiber and its distance from and angle with the target. Also, the effects differ according to the characteristics of the tissue, the extent to which the tissue absorbs or scatters the beam, and the cooling effect of the circulating blood in the target tissue. Less obviously, areas other than the target tissue might be affected because of beam scatter and conduction of thermal energy by the tissues. The depth of penetration does not necessarily reflect the laser effect, i.e., as the laser beam is generated, diffusion of energy takes place laterally, and the extent of the temperature rise decreases in proportion to penetration. In other words, there will be an area at which penetration occurs but significant temperature rise and coagulation does not.

In contrast to electrocautery, which produces a shallow, bowl-shaped necrosis with irregular and downward borders, the Nd:YAG laser induces a deep, homogeneous, cone-shaped area of necrosis with clearly demarcated lateral borders beyond which the tissue is intact. Further, in laser-treated tissue, the blood flow decreases to near-baseline levels or stops throughout the coagulated area, and vascular stasis occurs in the erythematous zone encircling the necrosis, whereas in tissue coagulated with electrocautery, no corresponding constant decrease in blood flow occurs. Thus, Nd:YAG laser irradiation produces a more extensive and homogeneous arrest of blood circulation in the treated area, so the risk of bleeding is substantially minimized. Again, in contrast to electrocautery, which, when used in the treatment of bladder tumours that may involve resection of a portion of the bladder wall, with a well-recognized risk of bladder perforation, laser therapy induces tu-

mour destruction without direct contact and depends on secondary slough of the coagulated area. Therefore, even with excessive doses of laser energy and complete transmural necrosis, the bladder wall maintains its structural integrity, so gross perforation is unlikely. It is worth remembering, however, that both the Nd:YAG laser and conventional electrocautery are instruments of thermal destruction, and with excessive energy the laser will produce the same kind of conduction thermal injury as does hot cautery to neighboring organs such as small bowel adjacent to the bladder.

With conventional electrocautery, lateral heat propagation declines on a gradual linear gradient, and adjacent tissues must recover from the ill effects of a diffuse, irregular conduction burn before healing can begin. In contrast, with skilled use of the laser, thermal injuries can be confined within a narrow and sharply defined band, because thermal injury to adjacent tissues declines exponentially with distance from the center. Thus, pain and other irritative symptoms are significantly reduced during treatment and subsequent healing. Secondary slough of the coagulated area occurs within 1 or 2 weeks of surgery and reepithelialization is completed within 6 weeks.

Superficial bladder cancer

Surgical technique

The Nd:YAG laser is transmitted by a flexible fiber that is easily inserted through the working channel of a standard cystoscope, with the tip being directed by a modified Albarran apparatus. Because the Nd:YAG beam is invisible, an additional light source is employed to provide a coincident beam of visible white (xenon flash lamp) or red (helium-neon laser) light. The laser unit is powered by electrical current and usually necessitates the installation of a special power supply. In addition, an external water cooling system is required, and a special plumbing system may be necessary to provide drainage.

Nd:YAG laser energy directed to the bladder wall must be delivered over a period of 2–3 seconds with a power output of approximately 40 watts to produce necrosis to a depth of 2–4 mm. In practice, the fiber tip is directed to within approximately 5 mm of the tumor surface, and 2–3 seconds of application are usually necessary to attain the desired visible white discoloration indicative of adequate thermal destruction.

We usually begin treatment at the periphery of the tumor and the adjacent mucosa and carry it centrally. For somewhat larger tumors, the superficial necrotic pieces can be dislodged in order to attack the central portion. The total amount of energy is controlled by moving the fiber over the surface of the tumor as if one were painting, so that the laser is not applied to any target area for longer than 3–4 seconds. Thus, the thermal necrosis reaches no

deeper than the superficial muscle layer, and safe and effective treatment is achieved. Full-thickness necrosis is neither necessary nor desirable when treating superficial lesions.

The Nd:YAG laser is capable of coagulating vessels up to 0.5 mm in diameter. Consequently, hemostasis is usually adequate. Nevertheless, bleeding rarely occurs during treatment. The Nd:YAG laser, however, generally seems less effective than conventional electrocautery for obtaining hemostasis with vessels that are already bleeding. Other laser effects, including sealing of lymphatics around the tumor base and possible immunologic factors induced by laser energy are of relative unimportance or entirely speculative, respectively, when considering superficial bladder tumors.

In our experience, most areas of the bladder are accessible for laser treatment, although lesions at the bladder neck can be difficult to reach. For such cases, flexible instruments, which easily accept a laser fiber, can be used. Obturator nerve stimulation does not occur with laser therapy. Tumours larger than 2.5 cm generally are too large for laser treatment alone. Tumor debulking can be performed with electrocautery, followed by laser therapy, but this would negate the advantages of laser. The new McPhee resectoscope allows removal of tumor with a loop and a laser fiber passed beside the loop, and so may be ideal for such cases (Fig. 1).

Because of the reduced pain during laser therapy, we treat virtually all patients with local anesthesia, sometimes supplemented with intravenous sedation. Postoperatively, bleeding is minimal or nonexistent, and patients suffer only minor irritative voiding symptoms. Thus, there is no need for catheter drainage, and patients are treated on an ambulatory basis. We have not observed, nor have there been reports of a late bladder contractures or stricture of the ureteral orifice. Bowel perforation has been described, however, when excessive laser energy was applied [1, 2].

Because tumor destruction occurs without direct contact, there is no material available for histologic examination and assessment of tumor grade and stage. A definitive diagnosis of transitional cell cancer can be established with a cold-cup biopsy specimen taken prior to laser therapy, but this still does not permit staging, and grading may be inaccurate.

Therefore, several measures have been suggested. The thermally coagulated tumor mass can be dislodged and submitted for pathologic examination, but this is unsatisfactory because staging is inadequate. Urine cytology may help to determine the grade of the disease. Other authors have recommended a preliminary electrocautery resection followed by laser therapy of the tumor base [3] (See Fig. 1).

In general, we do not use these methods if the patient requires an adequate assessment of the grade and stage of the disease. In particular, we do not combine electrocautery with laser therapy, because the base of the tumor would not be included in the specimen, precluding adequate staging, and a preliminary electrocautery would obviate the potential for noncontact tumour destruction and the ability to perform the procedure without anesthesia.

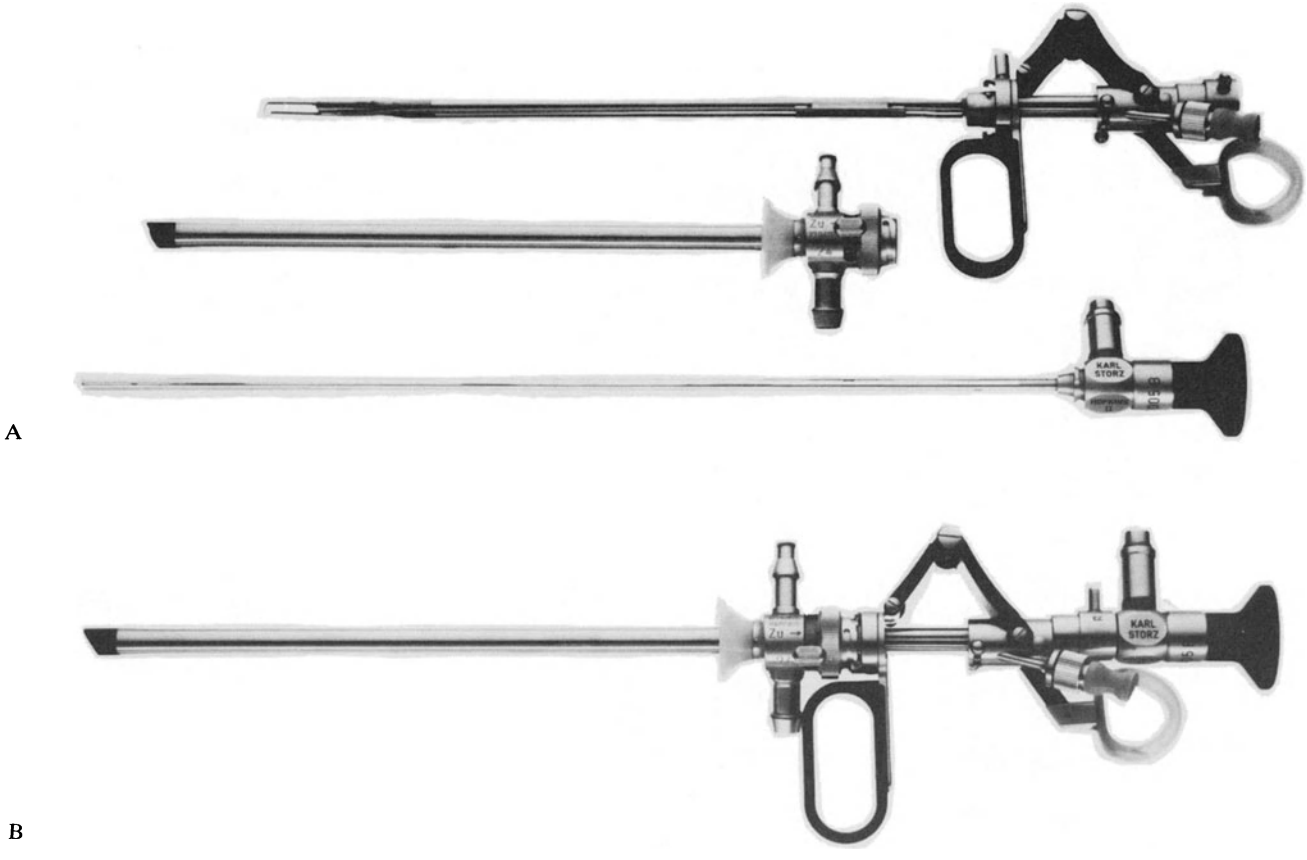

Figure 1. A: McPheee combined laser and high-frequency resectoscope. The bridge for the laser and the resectoscope loop is in the upper part of the figure. B: assembled instrument.

Results

The majority of patients with bladder cancer have superficial tumors that usually do not progress. Tumors recur, however, and the treatment should be directed at removing present tumors and preventing new ones. Ablation of the present tumor is adequately achieved with laser therapy if one follows the guidelines previously discussed. Certainly, such treatment has distinct advantages as well as some disadvantages (Table 1).

We frequently use laser therapy in patients known to have low-risk superficial disease who need only ablation of the present tumors and for whom no other form of therapy is entertained at the time of the evaluation. This group includes newly identified patients in whom cystoscopic evaluation reveals low-grade, noninvasive-appearing small papillary tumors emanating from a stalk, rather than sessile tumors, provided cytology results are negative. Certainly, we perform standard electrocautery resection and evaluate the bladder with selective biopsies that include the prostatic urethra if the patient has positive cytology, the tumor appearance suggests a high-grade lesion, or carcinoma in situ is suspected that is, if the patient is at high risk for invasive disease and there appears to be need for additional treatment such as intravesical bacillus Calmette — Guerin (BCG). We also use electrocautery resection when a tissue biopsy is required to assess the disease when the tumors appear invasive and for lesions of the prostatic urethra [4].

In properly selected patients, tumor recurrence or persistance at the site of laser treatment has been reported to occur in as few as 4% of patients [5,6]. In addition, several authors have claimed that Nd:YAG laser therapy is associated with fewer recurrences than is electrocautery resection, with reported rates in the range of 5% to 35% [2, 3, 7, 8,]. However, these data came from uncontrolled and nonrandomized studies that also were hampered by variability in patient selection as well as by insufficient numbers and length of follow-up. Lasers do have the capability to destroy tumors without direct contact, so, theoretically, and in contrast to electrocautery, tumor recurrence

Table 1. Advantages and disadvantages of Nd: YAG laser therapy in relation to electrocautery resection for superficial bladder tumors

Advantages	Disadvantages
Reduced pain	Does not provide tissue for diagnosis, grading, or staging
Absence of bleeding	Inadequate hemostasis for vessels larger than 5 mm
No obturator nerve stimulation	Bladder neck tumors relatively inaccessible
Decreased risk of perforation	Inadequate for tumors larger than 2.5 cm
No need for anesthesia	
Minimal postop symptoms	
No need for catheter	
Reduced risk of infection	
Outpatient surgery	

secondary to implantation of viable tumor cells would be prevented [9].

There have been two prospective studies in which serious attempts to address the issue of recurrence have been made. The first study, reported by Hofstetter et al. [1], included 65 patients with tumor stages T_a, T_1, or T_2 who were randomized for either conventional transurethral resection (TUR) or laser therapy. Patients in each group were further randomized to control (no other treatment) or adjuvant intravesical mitomycin C. The results were analyzed separately in patients with primary tumors ($n = 40$) and in those with recurrent tumors ($n = 25$). The recurrence rate was significantly reduced ($p < 0.0001$) in patients with primary tumors treated with laser therapy, whether or not adjuvant mitomycin was administered, compared with TUR-treated patients. The use of adjuvant intravesical mitomycin reduced the recurrence rate in both the primary and the recurrent tumor groups. In addition, unlike the case with TUR, no change from local to multiple tumor growth was observed after laser irradiation.

The second study, reported by Beisland and Seland [6], included 122 patients with bladder cancer up to stage T_2 who were randomized to either laser therapy ($n = 62$) or TUR ($n = 60$). Thirty-eight patients had previously had TUR, and 40 patients had multiple tumors. Rates of recurrence in the treated area were 5% in the laser group and 32% in the TUR group, a highly significant difference. Small tumors did not recur in either group, and larger stage T_1 tumors recurred only in the TUR group. Six of 10 stage T_2 tumors in the TUR group and 3 of 15 in the laser group recurred. Importantly, similar numbers of patients in the two groups had new disease in untreated areas. The authors concluded that the Nd:YAG laser was the best approach to stage T_1 tumors.

Both of these studies provide data suggesting that tumor recurrence is less likely with laser therapy than with TUR. However, Beisland and Seland's data do not agree with the data from Hofstetter's group that the recurrence rate is also lower in the nontreated areas of the bladder after laser irradiation. Furthermore, Beisland and Seland found no difference in local recurrence rates for patients with small tumors. In addition, it is unknown in both studies how many patients in the TUR group were treated with electrocoagulation only, as opposed to complete resection of tumors, and how many patients in the laser group were first treated with electrocautery resection for staging of the disease, followed by laser application to the tumor base. Further, disease variables such as positive cytology or the presence of carcinoma in situ were not considered. Thus, definitive clinical evidence for the contention that laser therapy prevents or decreases tumor recurrence is lacking.

Invasive bladder cancer

The Nd:YAG laser, in doses of 45–50 watts applied for 4–5 seconds, is capable of producing transmural necrosis of the bladder wall with preservation

of its structural integrity [8]. Thus, laser treatment of muscle-invasive lesions would appear feasible.

This approach has several drawbacks, however, First, prior to laser therapy, TUR of the lesion is necessary for staging and debulking purposes. Thus, the possible benefits of noncontact therapy are unavailable. Second, the surface of the tumor, particularly after previous TUR, is irregular and shaggy. Thermal changes on the tumor surface are therefore difficult to see and the laser beam needs to be directed systematically to the entire tumour surface without dependence on visible changes. Thus, transmural necrosis may not be achieved in all the treated areas, and therefore, complete destruction of deeply invasive lesions may not be accomplished. Further, there is an increased risk of excessive application of laser energy, resulting in damage of adjacent bowel [10]. Third, an obvious concern is that the tumor surface could reepithelialize with subsequent negative biopsies and cytology studies, despite the continued presence of viable tumor within the bladder wall. Fourth, accurate staging is of paramount importance, since deeply invasive lesions (e.g., stage C tumors) are not amenable to laser therapy, yet it is well recognized that clinical understaging occurs in a significant number of patients with muscle-invasive lesions despite the availability of new diagnostic imaging techniques such as computer tomography or ultrasonography [11]. Thus, laser use has a definitive associated risk of undertreatment.

Several investigators have attempted definitive treatment of muscle-invasive bladder cancer with laser energy [1, 2, 6, 8, 12, 13]. Most of the available reports include only few patients, and the follow-up is usually less than 2 years. Nevertheless, review of these studies reveals that the likelihood of tumor control decreases with increasing tumor stage. Shamberg et al. [13]. reported on eight patients with T_2 lesions and on 10 with T_3 lesions who were treated with the Nd:YAG laser and were followed as long as 2 years. Tumor recurrence was observed in 33% of the patients with T_2 tumors, and resistant or residual tumors were found in 80% of the patients with T_3 lesions. In another study that included a relatively large number of patients [10], four of five with B_1 tumors and three of six with B_2 tumors had normal post-treatment biopsies. Further, local residual tumor was present in three of four patients with stage C tumors and in all of the six patients with metastatic cancer. Although one patient suffered a sigmoid colon perforation, and clear palliative benefits could not be determined, the author concluded that adequate debulking and perhaps a reduction of bleeding episodes had been accomplished.

The limitations of laser therapy in the treatment of invasive tumors are further illustrated in a study reported by Tarantino et al. [12] in which 19 patients with cancer invasive into the lamina propia or muscle were treated with the Nd:YAG laser prior to standard cystectomy. Six operative specimens contained residual tumor with no change in stage, six patients with clinical T_2 lesions were pathologically upstaged when tumor was noted in the perivesical fat, six patients were downstaged to T_0, and one was found to have carcinoma in situ. Interestingly, this study also reported on another 53 patients with

similar invasive lesions in whom cystectomy was not part of the initial treatment. These patients were divided into three groups, and the follow-up was from 3 to 24 months. Twenty-five patients (group 1) were primarily treated with the Nd:YAG laser for all grades of invasive disease. Of these, 21 patients were evaluable and 14 (66%) were found to be free of disease or downstaged to superficial cancer. Fourteen patients (group 2) were treated primarily with the laser and subsequently with intravesical chemotherapy. Of these, 13 patients were evaluable, and 10 (76%) were either free of disease or downstaged to superficial cancer. Fourteen patients (group 3) with a history of multiple transurethral resections were treated with laser alone. Of these, 10 patients were evaluable and six (60%) were free of disease. Unfortunately, this report does not specify the number of patients with muscle-invasive cancer.

Another study that suggests laser therapy may prove useful as an adjunctive treatment of invasive bladder cancer is that of Beisland and Seland [6], who reported on 15 patients with T_2 lesions treated with TUR followed by the Nd:YAG laser. Tumor recurrence was observed in only three patients, as opposed to 6 out of 10 patients with similar lesions treated with TUR alone. This was a prospective, randomized study with a follow-up of 2 years. The authors concluded that for stage T_2 lesions, the combination of TUR and laser therapy was superior to TUR alone.

Cancer of the upper urinary tract

Transitional cell carcinoma of the upper urinary tract has traditionally been managed by nephroureterectomy with removal of a cuff of the bladder. However, open parenchymal-sparing conservative surgery for certain cases has been advocated by several investigators [14–17]. More recently, with the introduction of endourologic methods, closed ureteroscopic and percutaneous renal surgery have evolved as a logical extension of conservative treatment [18–24]. Thus, much as in the case with bladder cancer, selected cases of renal pelvic or ureteral transitional cell cancer might be amenable to endourologic laser treatment.

Experimental studies in animal models performed by our group [25] and by others [26, 27] have demonstrated that transmural necrosis and perforation of the ureteral and renal pelvic wall results when the Nd:YAG laser is used in doses similar to those applied in treating superficial tumors of the bladder because of the smaller thickness of the upper tract wall (1.0–1.5 mm). The optimal laser effect was achieved with a power less than 25 watts that was limited to no longer than 3 seconds. However, in the case of the ureter, direct application of these findings to a clinical setting is difficult, because the laser beam would be directed tangentially and not at a right angle to the tumor surface. Tangential application reduces the risk of perforation, but it also limits effective application of the laser to the tumor's distal side. Thus, effective treatment may require dislodgement of the treated area of the tumor

so that shadowed areas are exposed. Hence, power of up to 35 watts can be used in the ureter [8]. Similarly, when the tumor is located in the intramural ureter or in renal calix, higher laser powers can be used safely, because the surrounding muscular layer of the bladder or the renal parenchyma, respectively, decrease the risk of perforation. A percutaneous nephrostomy tube [19] or indwelling ureteral stent [8] should be routinely used in the postoperative period because of the risk of perforation.

Ureteral cancer

Several investigators have reported on the transureteroscopic use of laser therapy for ureteral tumors [3, 5, 8, 18, 19, 28–30]. In most of the studies, however, the follow-up was inadequate and the number of patients was small or the cases was anecdotal. Further, laser therapy was usually preceded by resection of the tumor by cold-cup biopsy forceps or electrocautery for assessment of the grade and stage, and the tumors were usually single, small, low-grade, and superficial, and were localized in the distal ureter. However, a study by Schilling et al. [29] that included 13 patients with a total of 16 ureteral tumors, all in the lower ureter, and a follow-up from 3 to 31 (mean 23) months has been reported. In this study, no local tumor recurrences were observed, with the exception of one heterotropic recurrence distal to the original tumor site. Biopsy specimens were first obtained through the ureteroscope, and laser energy was administered as a definitive treatment only if the tumor was of low grade and superficial on permanent histologic sections. The authors concluded that radical measures such as nephroureterctomy as a first step are no longer necessary and that the laser does not preclude subsequent surgery.

Several reports have emphasized the direct correlation between the grade and stage of upper-tract tumors and that the likelihood of tumor recurrence directly correlates with the grade and stage [14–19]. In addition, ureteroscopy enables direct examination of the lesion as well as biopsy for a tissue diagnosis. Thus, it is possible to say that transureteroscopic laser therapy of selected tumors, that is, single, superficial, low-grade, and small lesions, might be feasible, particularly if the lesion is located in the distal ureter where ureteroscopic access is more readily achieved.

Renal pelvic cancer

Only a few authors have reported on the use of laser therapy for the treatment of renal pelvic tumors, and, much as in the case of ureteral tumors, most reports include only anecdotal cases in which the tumors were treated ureteroscopically [3, 28]. We have used this approach in five patients. However, destruction of the tumor was incomplete in three, and the renal pelvis could not be reached in two [18]. As evidenced by our experience [18], and as the results of other investigators have suggested [16, 22, 23], adequate access to the renal pelvis and destruction of the tumor are accomplished better percutaneously than ureteroscopically.

Our group [18, 19, 31] and other investigators [20–22] have reported preliminary success with the percutaneous approach for the treatment of renal pelvic tumors. Laser therapy was not used by the other authors, however. Following is a description of our experience with this modality.

Fourteen patients with renal pelvic tumors were treated by percutaneous resection. They were selected for this treatment because of a solitary kidney (three patients), bilateral synchronous tumors (one patient), renal insufficiency (three patients), poor surgical risk (two patients), or preoperative evidence of a single, low-grade, superficial tumor (five patients) (Table 2). Random cold-cup biopsies of the renal pelvic mucosa were obtained prior to resection of the tumor. At the end of the procedure, the tumor bed and any remaining suspicious areas were fulgurated with a Bugbee electrode, and a nephrostomy tube was inserted. At this time, three patients were found to have invasive tumors, and they were treated with standard nephroureterectomy a few days later. The tissue removed by biopsy included muscle, fat, or renal parenchyma, and the specimen retained enough architectural detail to allow adequate assessment of the grade and the invasiveness in 11 patients. The tumors were graded according to Koss [32] and staged according to Cummings [14] (Table 3). Second-look nephroscopic examination and random

Table 2. Characteristics of patients treated with Nd: YAG laser for renal pelvic carcinoma

Characteristics	Number of patients
Age: Range: 51–83 years	
Mean: 69 years	
Sex: Male	8
Female	6
Previous treatment (ipsilateral tumor)	
Partial nephrectomy	1
Pyelotomy and excision	1
Transureteroscopic resection[a]	5
Contralateral kidney	
Previous nephrectomy[b]	3
Synchronous TCC[c]	1
Impaired function	3
Normal	7
Other TCC[d]	6
Poor surgical risk	2

[a] Complete resection proved to be impossible in three patients, and the renal pelvis could not be reached in two.

[b] For TCC in two patients and for benign disease in one.

[c] Treated with nephroureterectomy.

[d] With history of or concurrent TCC elsewhere in the urinary tract. Three patients had synchronous TCC in the distal ipsilateral ureter, two were treated with transureteroscopic resection, and the other was treated with distal ureterectomy and ureteroneocystostomy.

Table 3. Characteristics of renal pelvic transitional cell cancer

Pt.	Selective preop urine cytology	Visible multifocal disease	Sessile architec.	Largest diameter (cm)	Koss grade	Cummings stage	Random biopsies
1	–	Negative	–	1.0	I	I	Negative
2	+	Positive	–	1.0	II	I[a]	Moderate atypia
3	+	Positive	+	2.0	II	I[a]	Ca in situ
4	+	Positive	–	1.0	II	II	Ca in situ
5	–	Positive	–	3.0	III	III	Not done
6	–	Negative	–	2.5	II	I[a]	Not done
7	+	Positive[b]	+	3.5	III	II	Severe atypia
8	–	Negative	–	1.0	I	I	Negative
9	–	Positive	–	1.0	I	I	Negative
10	–	Negative[b]	–	1.5	I	III	Negative
11[c]	+	Positive	+	3.5	III	III	Ca in situ
12[c]	+	Positive	+	3.0	III[d]	II	Ca in situ
13	–	Negative[b]	–	1.5	I	I	Negative
14[c]	+	Positive[b]	+	2.0	III	III[e]	Ca in situ

[a] Specimen did not include deep layers (muscle, fat, or renal parenchyma) or did not have sufficient architectural detail to allow adequate assessment of invasiveness.

[b] Tumor originated in a renal calix.

[c] Patient underwent immediate nephroureterectomy with resection of nephrostomy tract when invasive tumor was discovered in tissue removed percutaneously.

[d] Patient had squamous cell carcinoma.

[e] Patient had a microscopic focus of metastatic disease in a regional lymph node removed at time of nephrectomy (stage IV disease).

biopsies of the renal pelvis to discover and ensure the removal of any residual disease was performed in 10 patients through the already established nephrostomy tract several days after the original surgery. Biopsies were available for review in seven patients and were positive for microscopic residual disease in three. Irradiation with the Nd:YAG laser (each pulse limited to 15–20 watts for 2 seconds) to the tumor bed and suspicious areas was performed in eight patients at this time.

After the second look, seven patients received intracavitary therapy administered through the nephrostomy tube. One patient was given one dose of mitomycin C (20 mg in 50 ml water). The other six patients received BCG on a weekly basis. The nephrostomy tube was removed after completion of the therapy, except in four patients on whom a third-look nephroscopy was carried out prior to removal of the tube. BCG granulmas were found in one patient at this time (Table 4).

With a follow-up of 5 to 45 months (mean 19), recurrences have been observed in the renal pelvis and ipsilated ureter in three patients and in the renal pelvis alone in two, from 4 to 9 months after the initial surgery. One patient developed distant retroperitoneal metastases 19 months after the initial resection, which was followed by immediate nephroureterectomy because of invasive disease. Recurrence was virtually confined to patients with multifocal, high-grade, sessile, invasive, or larger than 2 cm tumors who, in addition, had mucosal abnormalities on random biopsies, positive preoperative cytology, or a history of concurrent transitional cell cancer in other segments of the urinary tract (Table 5). Our results indicate that a percutaneous operation adequately resects small, well-localized superficial tumors. However, for high-grade invasive tumors, this approach does not provide adequate

Table 4. Supplemental therapy

Pt.	Second look	Nd: YAG irradiation	Intracavitary therapy (doses)	Third look
1	NED[a]	No	None	Not done
2	NED[b]	No	None	Not done
3	Not done	No	None	Not done
4	NED	Yes	BCG (8)	NED
5	NED	Yes	Mit c (1)	Not done
6	1 focus	Yes	BCG (3)	NED
7	NED[b]	Yes	BCG (2)	Not done
8	NED[b]	Yes	BCG (2)	Not done
9	1 focus	Yes	BCG (2)	NED
10	1 focus	Yes	None	Not done
11	NED	Yes	BCG (8)	NED

[a] NED-no evidence of disease including cytology study of urine obtained through nephrostomy tube.

[b] No biopsies were obtained.

extirpation, even though the tissue removed may include deep layers, because deep thorough resection is precluded by the relatively thin renal pelvic wall and the associated risk of perforation. Equally important, adequate margins of resection may be difficult to determine percutaneously in patients with carcinoma in situ or high-grade invasive lesions, given the multifocality that appears to be inherent in such lesions.

Second-look procedures in which resections of residual suspicious areas are preformed appeared to be important to ensure complete extirpation of the tumor. Nd:YAG laser irradiation of the tumor bed also appeared to help in preventing recurrence (Table 6). It is conceivable that laser irradiation contributed to complete ablation of superficially invasive lesions in some of our patients by extending the depth of the treatment. However, our series is small, and without further data, laser use cannot be recommended categorically. Intracavitary BCG was well tolerated and appeared to be safe, and tumor recurrence was observed in 80% of the patients who did not receive BCG as opposed to 16.6% of those who received BCG (Table 6).

Two concerns have been expressed in early reports of percutaneous treatment [19, 21, 22]: the risk of local tumor spillage and the risk of tumor implantation in the nephrostomy tract. In our series, neither event was observed, nor were there any cases of local recurrence outside the urinary tract that were attributable to percutaneous resection. However, ureteroscopic resection may obviate the risks of nephrostomy tract implantation. Thus, we would advocate ureteroscopic resection first and reserve percutaneous management for patients in whom ureteroscopic resection is not sufficient or possible.

Table 5. Correlation between tumor characteristics and renal pelvic tumor recurrence[a]

Tumor characteristics	No. of pts.	% local recurrence
Single/multifocality (1)	5/6	0/66.6
Low/high grade[b]	5/6	0/66.6
Superficial/invasive[c]	4/4	0/75
Papillary/sessile	8/3	25/100
Size 2 cm/2 cm	7/4	28.5/75
Negative/positive random biopsy[d]	5/4	20/75
Negative/positive preop cytology	6/5	16.6/80
Negative/positive other TCCA	6/5	16.6/60

[a] Excluded are three patients who underwent nephroureterectomy immediately after percutaneous resection.

[b] Grade I considered low; grades II and III considered high.

[c] Stage II considered invasive. Included only those patients in whom adequate assessment of invasiveness was possible.

[d] Moderate to severe atypia or in-situ carcinoma. Excluded are two patients who did not have random biopsies.

Table 6. Supplemental therapy and results[a]

Supplemental therapy (no. of pts.)	Ipsilateral renal pelvis recurrence Yes (%)	No (%)
Second look plus resection of suspicious residual disease		
Yes (7)	2 (28.5)	5 (72.5)
No (4)	3 (75)	1 (25)
Nd: YAG irradition		
Yes (8)	3 (37.5)	5 (62.5)
No (3)	2 (66.6)	1 (33.3)
Intracavitary BCG therapy		
Yes (6)	1 (16.6)	5 (83.3)
No (5)	4 (80)	1 (20)

[a] Excluded are three patients who underwent nephroureterectomy immediately after percutaneous resection.

Hematoporphyrin photosensitization and the argon-dye laser in the treatment of superficial bladder cancer

Some chemical compounds (photosensitizers) are capable of destroying tissue in the presence of light and oxygen, a phenomenon noted first by Raab [33] in 1900, when he demonstrated the lethal effects of acridine dye on *Paramecium* exposed to light. This is now termed *phototherapy* or *photodynamic therapy*.

An ideal photosensitizer would be a nontoxic drug that is taken up or retained selectively by malignant tissue and that would absorb light at wavelengths that are not absorbed by normal tissue. No such drug exists at the present time. However, several potentially useful photosensitizers are available, i.e., fluorescein, eosin, tetracycline, acridine orange, and several porphyrins. Among photosensitizers, hematoporphyrin derivative (HPD) is the most relevant and best studied for both tumor localization and treatment because of its greater affinity for malignant tissue. HPD is not selectively absorbed by tumors; normal tissue, including skin, and inflammatory or regenerating tissue also absorb HPD significantly. Nonetheless, relative to normal urotherlium, invasive bladder cancer and in-situ carcinoma preferentially take up HPD [34].

HPD is a mixture of several porphyrins of which only one, dihematoporphyrin ether (DHE), is known to be active as a tumor photosensitizer. DHE itself does not fluoresce. However, injection of DHE into animals produces fluorescence in tumors. This is believed to be the result of DHE absorption by tumor cells within which DHE disaggregates or is metabolized, or both. Thus, DHE may be important for tumor uptake and retention but appears to not be directly responsible for the fluorescence or photosensitizing effect.

The accepted mechanism of action of HPD phototherapy is an energy-transfer process in which singlet oxygen is produced, which causes irreversible oxidation of some essential cellular components [34]. At a microscopic level, photodynamic therapy of bladder cancer causes the tumor to become edematous, and within 4–7 days hyperemia and necrosis develop. These changes are most intense at 15 days and gradually resolve until reepithelialization occurs several weeks later [35]. Histologically, the earliest changes occur in perivascular regions, with congestion and infiltration of inflammatory cells. In addition, HPD localization studies have shown HPD in the endothelial cells of tumor capillaries. Thus, it would appear that vascular effects, and hence tumor ischemia, may be an important factor in the efficacy of photodynamic therapy [36].

The effectiveness of phototheray depends on the dose of HPD, the delay between drug administration and light delivery, the physiologic status of the tissue, and the rate, mode of delivery, and total amount of light given. The dose-response relation of HPD has not been clarified for clinical use in the treatment of bladder cancer, although doses of 2.5–5 mg per kilogram of body weight have been recommended [34]. The timing of light delivery after HPD administration has differed in the few studies dealing with bladder cancer. The therapeutic effect appears to reach its maximum at 3 hours after drug administration and then levels off [34]. However, most investigators treat within 48–72 hours [37, 38], although treatment at 3 hours and again at 48–72 hours, if necessary, has also been reported [34].

The proper light dose for maximal effect is also unknown. Any source of light may be used for HPD phototherapy, provided its wavelength matches closely the absorption of HPD. HPD has five major absorption peaks, all in the visible spectrum, ranging from 400 to 625 mm. Red light (630 mm) has been most often used in the clinical setting because it penetrates tissue for approximately 1 cm. However, absorption by HPD is poorest at this wavelength. On the other hand, shorter wavelengths of light, such as blue (400 mm), which corresponds to the highest absorption band of HPD, or blue-green (500 mm), which corresponds to the second high-absorption band, are associated with less tissue penetration, only 1–2 mm.

Extended light sources, such as incandescent lamps and mercury arcs, do not permit focusing of light with enough power into an optical fiber. Thus, delivery of light into the bladder is best accomplished with lasers because of their high-power density beam of a small diameter and their high coupling efficiency to optical fibers. The most commonly used system has an argonion laser to pump a laser operating with a dye (rhodamine B or DCM). This system produces light at a wavelength of 630 mm and 4 watts. The output from the laser is coupled to a single quartz fiber, which can be inserted through an endoscope. The distal end of the fiber can be altered to an optically flat end to produce an expanded core of light or to a 'lightbulb' tip for use in hollow organs such as the bladder.

Clinical results

Several authors have demonstrated that with focal delivery of light, HPD photoherapy can be effective for T_a and T_1 bladder lesions, with success limited to small tumors or in-situ focal carcinoma [37–39]. However, tumor recurrence has been observed in a substantial number of patients despite the short follow-up, which would indicate that this form of therapy is not able to prevent recurrences and that its effect, as in the case of the Nd:YAG laser or conventional electrocautery, is limited to destruction of present tumor.

Appropriate delivery of light to the entire bladder, in an attempt to reduce tumor recurrence, has also been attempted with the use of a lightbulb tip [38, 39]. With this technique (whole-bladder therapy), Benson [39], reported that complete disappearance of diffuse carcinoma in situ was achieved in all 15 treated patients according to evaluations carried out 3 months after therapy. Again, however, the persistence of associated T_1 lesions was observed, and, with a follow-up of 6–32 months, there were recurrences in eight patients, two of whom had five and six repeat treatments. Subsequent trials by the same author [40] with 30 additional patients with in-situ carcinoma produced similar results.

Complications or morbidity related to photodynamic therapy are significant. Patients may develop a marked cutaneous photosensitivity that requires avoidance of direct sunlight and adoption of protective measures for as long as 4 weeks after treatment. Also, patients uniformly suffer bladder irritability, and a decrease in measured bladder capacity is common, although these effects are only temporary [35, 38].

Summary

Nd:YAG laser therapy now has a well-defined role in the treatment of superficial bladder cancer, that is, it is indicated only when one needs to destroy present tumors. Available results suggest that tumor recurrence is reduced, but definitive evidence of this is lacking. The laser's main advantage is that the procedure is carried out without anesthesia on an outpatient basis, because it is a noncontact technique that is associated with minimal morbidity and reduced pain and bleeding. Nd:YAG laser use in invasive bladder cancer would appear to be adequate for palliation only. For this indication, its benefits must be compared with conventional palliative TUR and/or radiation therapy.

Laser therapy of tumors in the upper urinary tract is still in its infancy. Urothelial cancer is a multifocal disease [42], and the critical caveat, as in the case of bladder cancer, is tumor recurrence. Routine access to the upper tract and accurate assessment of the grade and stage of the tumor and the multifocality of the disease are of paramount importance and are not yet perfected.

Photodynamic therapy is an intriguing modality. It has much potential for future development, but at present, because of its reduced ability to control superficial cancer, particularly when compared with other available forms of treatment such as intravesical BCG, and because of its significant associated morbidity, its use remains investigational.

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8. Systemic chemotherapy in the management of bladder cancer*

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Carcinoma of the bladder is the second most common malignancy of the genitourinary system after prostate cancer. In the United States in 1988, there will be an estimated 46,000 new cases of bladder cancer and 10,400 bladder cancer-related deaths [1]. Approximately 70% to 80% of patients with transitional cell carcinoma (TCC), the most common histologic type in the United States, will present with superficial tumors (T_{15}, T_1). These patients are effectively treated with endoscopic surgery and intravesicular chemotherapy, and have a 5-year survival of of 65% to 85% [2]. In contrast, patients presenting with tumor invading into or through the muscle layer of the bladder wall (T_2, T_3, T_4) have a worse prognosis. Despite radical cystectomy, with or without radiotherapy, more than half of patients will relapse with metastatic disease [3] and the overall 5-year survival for patients with muscle involvement ranges from 10% to 45% [3, 4]. The pathologic stage of the primary tumor correlates most closely with the frequency of regional lymph node involvement and the development of distant metastases [3, 4]. P_{15} and P_1 carcinomas have a low probability of developing either lymph node metastasis (<5%) or distant dissemination (<10%). This incidence increases with progressive P stage such that about 40% of patients with P_4 tumors will have regional lymph node involvement, and over 60% will develop distant metastasis. Even microscopic lymph node involvement results in a 5-year survival of only 7% to 17% [4].

During the last 10 years, a multitude of trials investigating the efficacy of chemotherapy in TCC of the bladder have been reported. Combination regimens have produced long-term survival in patients with metastatic disease. Chemotherapy in combination with surgery and/or radiotherapy is now being used to treat advanced node-negative local disease in an effort to improve survival. The exact role of combined modality therapy, however, is

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still undefined. This paper will review the development of chemotherapy in bladder cancer, the use of combination regimens in recurrent or metastatic disease, and the developing role of combined modality therapies in locally advanced disease.

Response criteria

Many phase I and II chemotherapy trials of patients with advanced bladder cancer are difficult to interpret because of imprecise response criteria [5]. These inaccuracies have led to widely divergent response rates for the same agents. In 1976 Yagoda proposed more exact response criteria [6, 7]. In 1985, response criteria for urothelial tumors were outlined at the Consensus Development Conference on Guidelines for Clinical Research in Bladder Cancer (Table 1) [8]. *Clinical complete response* (cCR) is defined as the complete disappearance of all clinical, radiographic, cytologic and biochemical evidence of disease, including negative cystoscopy and biopsy. A *pathologic complete response* (pCR) requires the histologic confirmation of the absence of residual disease after exploratory laporotomy and/or cystectomy, or biopsy

Table 1. Response criteria for urothelial tract tumors

Complete remission (CR)
Complete disappearance of all clinical evidence of tumor on physical examination, x-ray, sonogram, CT scan, etc., and biochemical evaluation for 1 month.

Clinical CR (cCR): Complete disappearance of all clinical evidence of known disease sites proven by physical examination, x-rays, CT scans, radionuclide tests, biochemical parameters, cystoscopy with biopsy, and urine cytology.
Pathological CR (pCR): Surgical restaging with adequate biopsy specimens revealing no evidence of disease either by exploratory laparotomy and/or cystectomy, thoracotomy, or biopsy of sites of known previous disease.
Surgical CR (CRs): Surgical restaging with residual disease found that could be completely resected, rendering the patient free of disease, such patients may have been, before surgical evaluation, in any 'clinical' response category, even PROG.

Partial remission (PR)
Greater than 50% decrease on physical examination or radiography of the summed products of the perpendicular diameters of all measured lesions for 1 month. No simultaneous increase in size of any lesion or the appearance of any new lesions may occur. Abdominal and pelvic masses should be measured by CT scan and should be at least 2.5 cm in diameter. Similarly, malignant hepatomegaly greater than 3 cm should be measured by CT scan or ultrasonography

Minor response (MR)
25% to 49% decrease in the summed products of measured lesions for 1 month.

Stabilization (STAB)
Less than a 25% decrease or increase in tumor size for a minimum of 3 months.

Progression (PROG)
Greater than 25% increase in the sum of all measured lesions for greater than 1 month, the appearance of new lesions, or a mixed response.

of sites of known previous disease, such as bone. A *surgical complete response* (CRs) is defined as the complete resection of all residual viable disease after a chemotherapy-induced remission. The clinical stage prior to surgery may be cCR, partial remission (PR), or minor response (MR), and the operation is often performed to clarify tumor status following chemotherapy. These categories parallel the strategy in the treatment of patients with germ-cell tumors [9, 10]. These definitions of complete response and those for partial response, minor response, stable disease, and progression (Table 1) are used in this review.

Single-agent trials

A variety of chemotherapeutic agents have exhibited activity in TCC of the bladder. Only the most important agents are reviewed here. Cisplatin, methotrexate, doxorubicin, and vinblastine sulfate have been shown to induce remissions [7, 11]. Nevertheless, the majority of responses are PR and last from 3 to 5 months [7, 11, 12]. CR occurred rarely, and almost never in bone metastases or locoregional disease sites [7, 11].

Cisplatin

Cisplatin (DDP) is a heavy-metal, non-cell-cycle-specific drug that functions as an alkylating agent by inhibiting DNA, probably by intrastrand crosslinkage. For bladder cancer, it is usually administered at a dose of 70 mg per square meter IV every 3 to 4 weeks. Other schedules with doses of 50, 100, and 120 mg per square meter result in similar proportions of responses [11, 13, 14]. More than 320 patients with TCC have been treated with DDP and responses (CR plus PR) occur in about 30% [7, 11]. Responses of patients to DDP are usually partial and occur within 2 to 5 weeks of the start of therapy. If no response occurs, treatment should be changed. PR will last between 4 to 6 months. DDP appears to be most effective in soft-tissue metastases; responses in osseous sites are unusual [7, 11].

The major toxicities of DDP are renal and auditory dysfunction, both of which tend to be more severe in older patients with underlying kidney disease and presbyascusis. Nausea and vomiting can generally be controlled. Other side effects include hypomagnesemia, peripheral neuropathy, and diarrhea. Adequate hydration is necessary during treatment to minimize nephrotoxicity.

Methotrexate

Methotrexate (MTX), an antifolate, is a cell-cycle and phase-specific agent and binds to the enzyme dihyrofolate reductase, inhibiting the synthesis of thymidylic acid, DNA, and RNA, Early trials of MTX in recurrent bladder cancer used a variety of doses, schedules, and routes of administration,

including oral, IV, intravesicular, and intraarterial [15]. The overall proportion of responses, often not assessed by the measurement of bidimensional measurable disease, ranged from 0% to 38% [5]. In 1981, Natale et al., reported 42 patients with measurable indicator lesions treated with either high-dose MTX (250 mg per square meter followed by leucovorin rescue) every 2–3 weeks or low-dose MTX (0.5–1.0 mg/kg weekly) [16]. Only one patient responded in the high-dose group (a PR lasting 5 months), while 10/33 (30%) of patients receiving low-dose MTX achieved PR. The median duration of response was 6 months. Oliver et al. reported that 9/21 (43%) patients with measurable metastatic disease achieved either a CR or PR, using the response criteria as defined by Yagoda [17]. Similar to Natale et al., the median duration of response was 6 months.

Of 236 patients with recurrent or metastatic TCC reported to have been treated with MTX, 68 (29%) achieved a major response [7, 11]. Tumor regression generally begins by the third to fifth dose, and the median duration of response is 3–6 months [11, 16]. Some data suggest that MTX may be more effective than DDP for locoregional disease [15]. The optimal dose for MTX has not yet been determined. Yagoda noted that the proportion of response in 57 patients treated with high-dose MTX (100 mg per square meter) was 45%, suggesting that higher doses may be more active [11]. A randomized trial will be necessary to determine if high-dose MTX (100–200 mg per square meter) is any more efficacious than low-dose MTX (30–40 mg per square meter).

MTX is protein bound, excreted unchanged in the urine, and freely diffuses into body fluids. Therefore, caution should be taken in treating patients with abnormal renal function or with a pleural effusion or ascites. Special care should also be observed in patients with a long ileal conduit, since reabsorption of the drug may occur through the conduit wall, producing delayed clearance and enhanced toxicity [15]. The major toxicities of MTX include myelosuppression and anemia, oral mucositis, gastrointestinal ulceration, and bleeding.

Doxorubicin

Doxorubicin (Adriamycin, ADR) is an anthracycline antibiotic with multiple mechanisms of action, including intercalation between DNA nucleotide pairs. It is maximally cytotoxic in the S-phase but can effect all phases of the cell cycle. It is most frequently administered at a dose of 30–75 mg per square meter IV every 3 weeks [7, 18]. Early trials (which included MR as a major response) reported proportions of remissions as high as 35% [19]. However, Yagoda et al. reported a major response (CR and PR) in only 5/35 (14%) patients [18]. A randomized trial of ADR versus ADR plus DDP by the Southwest Oncology Group (SWOG) showed that 8/41 (19%) responded to ADR versus 43% (16/37) for the combination [20]. In one review an overall percentage of response of 17% has been observed [7]. Remissions rarely

occur after two to three doses and are more frequent in soft tissue. The median duration of response is 3–4 months and CR is again rare [11].

The toxicity of ADR includes nausea and vomiting, anorexia, alopecia, and myelosuppression. The major dose-limiting side effect is a congestive cardiomyopathy, which increases in incidence with accumulated dose [21]. Therapy is containdicated in patients with a decreased cardiac ejection fraction (45%), cardiomegaly, or congestive heart failure. As a result, some elderly patients with bladder cancer who have concurrent heart disease cannot receive ADR.

Vinblastine

Vinblastine sulfate (VLB) is a vinca alkaloid that inhibits mitosis by cell-cycle arrest in metaphase. At MSKCC, 5/20 (18%) patients achieved a PR, which lasted 2–5 months [22]. The dose of VLB was 0.10 or 0.15 mg/kg (equivalent to 4–6 mg per square meter) IV every week. Toxicity is generally mild, but includes myelosuppression and a peripheral or autonomic neuropathy.

Other agents

The results of some other single-agent trials are listed in Table 2. Newer agents with possible activity include gallium nitrate [23, 24] and the cisplatin analog carboplatin [25, 26]. Further trials with these agents are necessary before determining their roles, if any, in the treatment of bladder carcinoma.

Combination regimens

A variety of combination regimens based on DDP and MTX, the two most active single agents in TCC bladder carcinoma, have been evaluated. Drug dose and schedule were chosen either empirically or on the basis of data

Table 2. Single agents for urothelial tract tumors

	Number of patients	Percent CR + PR	Ref.
Vincristine	31	10	11
Cyclophosphamide	98	31[a]	7
5-fluorouracil	141	17[a]	7
Mitomycin-C	42	13[a]	7
Gallium nitrate	16	32	23, 24
Carboplatin	46	22	25, 26

[a] Reflects early trials using varied dose, schedules, and response criteria.

obtained from animal models [27]. Few studies are randomized and most contain small numbers of patients [7, 11, 28].

DDP in combination with other agents has been extensively studied [11]. The addition of cyclophosphamide (CYT) to DDP does not result in increased antitumor activity when compared to DDP alone [7, 11, 29]. An early report from MSKCC recorded a 43% CR plus PR respose rate in 35 patients treated with this combination [28]; of 102 cases reported in the literature, however, the proportion of responses is only 25% [7, 11]. The National Bladder Cancer Collaborative Group A (NBCCGA) conducted a randomized trial comparing DDP alone with the combination of DDP plus CYT. Ten of 50 (20%) patients responded to DDP alone, while only 7/59 (12%) responded to the combination, causing the NBCCGA to speculate that CYT may actually inhibit the activity of DDP [29].

The combination of DDP and ADR, however, does appear to increase the proportion of responses in comparison to either agent alone [11]. Yagoda reported that 21/40 (53%) patients responded to DDP (70 mg per square meter) plus ADR (45 mg per square meter) given every 3–4 weeks [28]. As noted earlier, a randomized trial by SWOG of ADR (50 mg per square meter) and the combination of ADR plus DDP (each at 50 mg per square meter) every 3 weeks resulted in 19% and 43% response rates, respectively [20]. Recently, a high-dose intensive, 'chronobiologically-timed' two-drug induction regimen used ADR at 60 mg per square meter followed 12 hours later by DDP at 60 mg per square meter, repeated every 30 days for a total of 9 months. Eight of 35 (20%) evaluable patients experienced a cCR and 12 a PR (57% combined CR/PR response rate), after eight patients were excluded because of inadequate therapy. The median duration of response for patients with a CR was 6.5 months, but three patients were alive without evidence of disease at 36, 59, and 106 months after the initiation of chemotherapy [30].

Numerous trials have been conducted using the combination of DDP, ADR, and CYT [11]. The initial report in 1977 from the M.D. Anderson Hospital used CISCA (DDP 100 mg per square meter day 2, ADR 50 mg per square meter day 1, and CYT 650 mg per square meter day 1, repeated every 21 days). An 83% response rate (10/12) was observed [31], but with additional patients the proportion of responses decreased to 42% (17/41) [32, 33]. Yagoda reported responses in 13/28 (46%) patients using a dose schedule of DDP 70 mg per square meter, ADR 45 mg per square meter, and CYT 250 mg per square meter every 3–4 weeks [34]. Other investigators have noted response rates ranging from 13% to 82% using slightly different dosage [7, 35]. Overall, remissions occurred in 46% of 351 patients treated with these three agents [11]. Two randomized trials compared DDP, ADR, and CYT to DDP alone. Remission rates in the two trials were 35% (15/45) and 21% (9/42) for the combination versus 17% (8/48) and 16% (7/45) for DDP alone, respectively [36, 37]. Neither difference was statistically significant, although the proportion of CR in the ECOG trial was significantly greater in the combination regimen [36].

Similar to DDP, multiple studies have examined methotrexate in combina-

tion with other agents, including VLB, ADR plus CYT, and mitomycin C [7, 11, 38–40]. Randomized trials comparing MTX alone to MTX combinations, however, have not been performed. MTX combinations (with agents other than DDP) have response rates ranging from 31% to 39%, results whose 95% confidence limits overlap the response rates seen with MTX alone [7, 11].

The combination of MTX and DDP has resulted in higher response rates than either agent alone [11]. In five separate studies, the proportion of major responses ranged from 45% to 68% (Table 3), and a CR was observed in 7% to 23% of treated patients. Responses were observed at all sites of metastasis. The EORTC reported a median duration of response of 64 weeks for patients achieving a CR and 23 weeks for PR, with a median survival of 81 and 37 weeks, respectively [41]. Using higher doses of MTX and DDP, Carmichael and associates reported a 68% CR plus PR response rate in 19 patients with recurrent TCC, but remissions lasted an average of 21 weeks. The median survival for all responders was 54 weeks [42]. In the only randomized study comparing MTX plus DDP to DDP alone, the Australian Bladder Cancer Study Group reported responses in 45% and 33% of 100 evaluable patients, repectively [43]. This difference is not statistically different. The overall reponse rate for MTX and DDP combinations for advanced local disease is 46% in 160 patients, yet only 14% achieved CR [11].

M-VAC

With the above results as background, the two most active regimens (MTX plus VLB and DDP plus ADR) were combined into a four-drug regimen (M-

Table 3. Methotrexate plus cisplatin for urethelial tract tumors

	Number of patients	Percent CR	Percent PR	Ref.
MTX 40 mg/m^2 d8, 15[a] DDP 70 mg/m^2 d1	43	23	23	41
MTX 200 mg/m^2 d1[a] DDP 100 mg/m^2 d1	19	21	47	42
MTX 60–80 mg/m^2 d1[a] DDP 60–80 mg/m^2 d1	20	15	30	26
MTX 50 mg/m^2 d1, 15[b] DDP 80 mg/m^2 d2	49	7	39	43
DCM[c] 300–400 mg/m^2[b] DDP 50–70 mg/m^2 d1, 28	24	17	29	44

MTX = methotrexate; DDP = cisplatin.

[a] Cycled every 3 weeks.

[b] Cycled every 4 weeks.

[c] DCM = dichloromethotrexate; administered weekly to maximum tolerated dose, then every 2 weeks; DDP every 6 weeks.

VAC) (Table 4). In the initial report, Sternberg et al. reported a major response in 71% of patients (17/24) with 12 (50%) CRs [45]. In a recent update, 57/83 (69%) evaluable patients had a major response and 31 (37%) attained CR [46]. The median survival for patients with PR was 11 months; non-responders survived a median of 7 months. The median duration of response for CR was 36 months (range, 8–49+ months), and the median survival has not been reached after a median follow-up of 43 months. The 2- and 3-year survival rates for patients with CR, however, were 71% and 55%, respectively. Both CR and PR occurred at all sites of disease, including lung, lymph nodes, and bone, although CR was unusual in liver metastases (1/9). Of interest, 53% of 19 node-positive (N^+) patients without distant metastasis achieved a CR (2 cCR, 4 pCr, and 4 CRs) versus only 33% of 64 patients with nodal and distant disease. Toxicity with M-VAC was predominantly myelosuppression. The median white blood count nadir for the first cycle was 2600 cells/mm^3, with 32/91 (32%) having a WBC less than 2000. Myelosuppression was more severe in patients having received prior irradiation. Significant nephrotoxicity was unusual and increased in frequency with each cycle of chemotherapy. DDP had to be discontinued because of renal dysfunction in five patients. Nausea, vomiting, alopecia, and mucositis were also common. Neurotoxicity, transient hepatotoxity, diarrhea, and ototoxicity occurred rarely [46].

An integral part of this treatment plan is an extensive restaging following a median of four (3–6) cycles of therapy. Pathologic staging is equally important in defining both CR and PR. CT scans after therapy can be misleading, suggesting residual disease in an area that represents only fibrosis, or not

Table 4. Dose and schedule of M-VAC and CMV

	M-VAC			
	Day 1	Day 2	Day 15	Day 22
Methotrexate	30		30	30
Vinblastine		3	3	3
Adriamycin[a]		30		
Cisplatin		70		

	CMV		
	Day 1	Day 2	Day 8
Methotrexate	30		30
Vinblastine	4		4
Cisplatin		100	

All doses expressed in mg per square meter.

[a] For patients who have received prior pelvic irradiation, the starting dose is decreased to 15 mg per square meter.

M-VAC cycles were repeated every 28 days. CMV cycles were repeated every 21 days.

detecting residual microscopic disease in lymph nodes or at other previously involved sites. Similarly, a clinically normal bladder by cystoscopy and biopsy may have residual disease at the time of cystectomy. Thirty of 101 (30%) patients with advanced or metastatic TCC underwent definitive pathological staging following chemotherapy [47]. Eleven patients were found to have a pathologically complete remission (pCR) at the time of surgery. Three of these patients were clinically staged as PR (two patients) or progressive disease (one patient). Thirteen patients were found to have viable tumor (often microscopic) upon exploration and had the residual disease completely resected at surgery. These patients were classified CRs. When disease was found, but totally removed (CRs), two additional M-VAC cycles were given.

Of the 31 who achieved CR, 11 were categorized as cCR, and 10 as pCR, and 10 as CRs [46]. All 10 CRs patients were initially catagorized as having a clinical PR. Surgery consisted of nephrectomy (1), cystectomy (7), cystoprostatectomy (1) and bilateral thoracotomy (1). Of the nine patients with N_3-N_4 disease, seven experienced downstaging to N_0 and one to N_1. The median durations of response for cCR, pCR, and CRs were 26 months, 28 months, and 27 months, respectively. The median survival for both cCr and pCR has not been reached after 28 and 30 months; the median survival for CRs is 27 months [46]. Therefore, in patients achieving significant tumor regression, debulking of residual disease may also result in prolongation of survival. These are carefully selected cases, of course; however, all patients achieving PR will eventually die of disease.

Ten (18%) of the 57 responders experienced CNS metastases (3 cCR, 3 pCR, and 4 PR). Median time from the start of therapy to brain metastases was 11 months (range, 6–42 months), and median survival after diagnosis was only 2 months [46]. This pattern of CNS relapse has been seen with other combination regimens [38, 48], suggesting a survival benefit from the chemotherapy, thereby permitting the appearance of disease in sanctuary sites. Other sites of relapse or progression were bone (24%) and liver (17%) [46].

An analysis of prognostic factors for survival of 92 patients with metastatic disease treated with M-VAC at MSKCC was recently reported [49]. With a median follow-up of 33 months, 25 patients were alive (27%). Less extensive disease, a normal hemoglobin, an initial high Karnofsky performance status, and a low alkaline phosphatase were all found to be independent favorable prognostic variables.

By way of comparison, the Northern California Oncology Group (NCOG) developed a three-drug regimen using MTX, VLB, and DDP (CMV) [48] (Table 4). NCOG reported their results with CMV in 62 patients with metastatic disease [50]. Sixteen patients (26%) achieved a CR and 10 a PR, for a total response proportion of 42%. Similar to other studies using MTX and DDP, responses were noted at all sites of disease. Four patients achieved a CR following surgical removal of viable tumor. The median duration of response for CR was 11 months (compared with 28 months for MVAC). These results may be inferior to M-VAC or may be due to a difference in the extent

to which CR is restaged. A randomized trial would be necessary to evaluate these possibilities.

Adjuvant Chemotherapy

The high proportion of systemic relapses in patients with T_2, T_3, and T_4 lesions (>50%) and the poor prognosis for patients with nodal disease illustrate the need for adjunctive systemic therapy in patients treated for local disease. Despite the need to improve survival following radical surgery and/or radiation therapy only, a small number of classical adjuvant (i.e., postoperative) chemotherapy trials have been performed [15]. In a randomized study performed by the NBCCGA, 43 patients were randomized to receive DDP (70 mg per square meter) every 3 weeks following preoperative radiation therapy and subsequent radical cystectomy. Only 8/43 (19%) patients were able to complete all eight cycles of DDP, and the study was discontinued because of poor patient compliance. No benefit was observed in those patients treated with DDP [51, 52]. Perhaps more important, of 423 patients screened for protocal entry, 156 (37%) completed radiation therapy and surgery and were eligible for randomization, and only 83 (20%) were randomized [51]. These data imply that the program is not feasible for most patients and that the results are the consequence of substantial patient selection.

Other nonrandomized trials of adjuvant DDP with a small number of patients showed no improvement of survival [53, 54]. Two nonrandomized studies of high-dose MTX following resection reported an improved survival. Soquet treated 33 patients with T_3 or T_4 lesions, of which 31/33 (94%) survived more than 1.5 years, 18/20 more than 2.5 years, and 6/10 more than 3.5 years [55]. There were no controls, however, only seven patients were N^+, and 25 patients required only partial cystectomy, indicating a selection bias [15, 52]. Hall et al. gave MTX to 57 patients (33 $P_{2/3}$, 16 P_{3a}, 8 P_{3b}) following complete transurethal resection in 53 and partial cystectomy in three patients. The 1-year and 2-year survivals were 82% (45/57) and 59% (23/39), respectively [56].

The morbidity of intensive chemotherapy after cystectomy results in difficulty with recruitment to such trials. Therefore, many investigators have explored neoadjuvant (i.e., preoperative) chemotherapy, either alone or in combination with radiation therapy. Regimens such as M-VAC achieved downstaging of primary bladder tumours and prolonged control of distant metastases, suggesting micrometastases might be eliminated. In addition, patients receiving systemic chemotherapy might be spared an unnecessary cystectomy.

Neoadjuvant chemotherapy

There are major clinical inaccuracies in the staging of bladder cancer. Despite the use of the CT scan and MRI, the error in clinical versus pathological

assessment of depth of invasion and the extent of locoregional lymph node involvement ranges from 35% to 55% [57]. Staging errors dramatically affect the results of neoadjuvant studies. In addition, the extent of restaging following chemotherapy (i.e., cystoscopy, cystectomy, pelvic lymph node dissection) and the definition of CR will alter response rates.

Cisplatin followed by radiation therapy for locally advanced disease has been studied using different dosages and schedules. Sterenberg and Scher reviewed six trials and noted CR rates ranging from 21% to 80% [7]. In three of these trials, the CR classification was based solely on cystoscopy [58, 59]. In two of these studies, radical cystectomy was performed at 8 and 22 days; the proportion of pathologic CR in the bladder was 21% (5/24) and 27% (6/22), respectively [60, 61]. The NCI-Canada reported on 29 patients with clinical stage T_{3b} and T_{4a} bladder cancer who received DDP [100 mg per square meter every 2 weeks for 1–3 cycles (mean 2.6)] concurrent with either preoperative or radical radiation therapy. At either cystectomy or cystoscopy or both, 76% had no residual invasive disease compared to 24% of 28 patients in an immediately preceding historical control group who completed similar therapy without DDP [62]. The National Bladder Cancer Group (formerly the NBCCGA) reported on 70 patients (22 cT_2, 36 cT_3, and 12 cT_4) who were not candidates for radical cystectomy because the tumours were judged to be unresectable or the patient was not fit for a radical operation. Planned treatment consisted of eight cycles of DDP (70 mg per square meter) with full-dose radiation therapy. The CR rate for all patients was 77%: 88% for cT_2, 84% for cT_3, and 50% for cT_4. The median survival for the 22 patients with cT_2 lesions was over 4 years, as compared to 18 months for patients with cT_3 and cT_4 [63].

A number of trials have now been reported using the three- and four-drug regimens as initial therapy (Table 5). Scher et al. at MSKCC reported on 50 patients treated with M-VAC [64]. Initial staging included cystoscopy, CT scan and/or sonography, and urine cytology. Of the 50 entered patients, 1 was staged T_{1s}, 7 T_2, 28 T_3, and 14 T_4. Clinical CR, pCR, and CRs were defined as described above (Table 1). Clinical PR required a greater than 50% decrease in the size of a measurable lesion by cystoscopy and noninvasive staging, plus downstaging by two or more T categories, or a T_0 lesion by transurethal resection with a persistent T abnormality by noninvasive staging

Table 5. Neoadjuvant combination chemotherapy for urothelial tract tumors

Therapy	T stage	No. evaluable patients	Complete premission		Ref
			No.	%	
M-VAC	T_3, T_4	45	10	22	64
M-VAC	T_3	12	4	33	65
CISCA	T_3	17	4	24	66
ADR, DDP 5 FU, VM26	T_3, T_4	16	5	31	67

or positive urine cytology. Transurethral resection evaluation after M-VAC (1–6 cycles) in 44 evaluable patients revealed downstaging in 30 (67%), with 25 (57%) T_0 and 5 (11%) T_{1s}. Six of six (100%) cT_2 patients were downstaged to T_0 as compared to 5/12 (42%) cT_4. Forty-seven patients were evaluable for urine cytology; 22/37 (59%) with an initial positive cytology became normal, while 1/10 (10%) with initial negative cytology converted to positive. Overall, in 45 evaluable patients, the proportion of cCR was 22% (10/45) and of PR was 19% (16/45) [64]. Thirty-two patients underwent definitive pathologic restaging (22 radical cystectomy, 6 partial cystectomy, and 4 laporotomy with bladder biopsy and lymph node sampling). A pathological CR was achieved in 10 (31%): 9/23 (39%) cT_3 versus only 1/7 (17%) cT_4 achieved P_0 status. A comparison of transurethal resection T staging after M-VAC to subsequent P staging revealed that 9 (28%) were clinically understaged ($T < P$) and none were overstaged ($T > P$). The final response rate was 30% CR (4 cCR and 8 pCR) and 28% PR (7 cPR and 5 pPr) [63]. These proportions of response are similar to those seen in patients with advanced disease treated with M-VAC [46].

Simon et al. reported comparable results with M-VAC in 25 patients (Table 5) [65]. In a study from the Cleveland Clinic using neoadjuvant intra-arterial CISCA, 8 of 17 patients had clinical CR, but four of these had residual foci of carcinoma at cystectomy [66]. Similar results were reported in a trial using three cycles of a four-drug regimen of ADR, DDP, 5-fluorouracil, and teniposide (Table 5) [67].

Follow-up for these preliminary trials is too short to assess the impact of neoadjuvant chemotherapy on the management of locally advanced bladder cancer. M-VAC induces significant tumor regression of intravesical and locoregional TCC. It is of interest that three patients who presented with mixed histology had disappearance of TTC elements with only adenocarcinoma or squamous elements remaining [64]. Neoadjuvant M-VAC in the treatment of extravesical urinary tract tumors also demonstrated ineffectiveness against mixed histological tumors [68]. Finally, in the MSKCC study, 12 (25%) patients judged to have resectable tumors for which standard therapy would have required cystectomy retained their bladders [64]. In this regard, future trials at MSKCC and elsewhere will consider bladder preservation as an endpoint.

Summary

The treatment of bladder cancer is in a state of evolution. With the advent of effective chemotherapy, multimodal treatment planning is needed to ensure the best results. This requires the participation of the urologist, medical oncologist, radiologist, and radiation therapist in order to determine the optimal treatment stategy for each patient. Currently, radical cystectomy should be considered standard therapy. Neoadjuvant or true adjuvant chemotherapy

are still investigational. Randomized trials should be designed to define those patients who will benefit from combined modality therapy, the sequence in which it should proceed, and its impact on disease-free and total survival. Certain principles in patient management require emphasis.

1. The patient must be carefully staged prior to treatment and later restaged thoroughly; whenever possible pathologic confirmation is recommended. Following chemotherapy, all sites of measurable and evaluable disease should be reassessed. Patients with residual masses may have only fibrosis, or microscopic tumor, and complete resection may result in prolonged disease-free survival.
2. Cystectomy after chemotherapy appears to be indicated when this is the only site of disease. If a patient responds systemically with a CR, but has residual disease in the bladder, salvage cystectomy may translate into a prolonged survival. Similarly, a patient who relapses in the bladder following chemotherapy should have surgery. It is unclear if patients with initially unresectable disease who are downstaged (PR) to a resectble lesion should undergo surgery or be consolidated with radiation therapy.
3. Adequate renal function is needed to give optimal doses of chemotherapy. Patients with ureteral obstruction often benefit from a nephrostomy tube. The creatinine clearance may improve following urinary diversion to allow full-dose chemotherapy [50].

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9. Mesenchymal-Epithelial Interactions in the Growth and Development of the Prostate*

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Introduction

The ductal networks within the prostate originate from solid epithelial outgrowths (prostatic buds) that emerge from the endodermal urogenital sinus (UGS) immediately below the developing bladder and grow into the surroundings mesenchyme (loose undifferentiated fetal connective tissue). In the human fetus, the first epithelial buds arise from the prostatic urethra around the 10th week of gestation [1–5]. The ducts grow rapidly in length, arborize, and canalize. By 13 weeks there are approximately 70 primary ducts, some of which exhibit secretory cytodifferentiation [1, 3]. The prostatic buds arise from different parts of the prostatic urethra in five separate groups in humans [1]. This observation led Lowsley to originally propose the concept of prostatic lobes. In mouse fetuses, prostatic buds appear on the 17th day of gestation (vaginal plug = day zero), while in fetal rats they appear 1 to 2 days later [6]. In the mouse one to three main ducts per side emerge from the ventral aspect of the UGS, while about 20 to 25 ducts per side emerge from the dorsolateral aspect of the UGS [7]. These two groups of ducts will form the ventral and dorsolateral lobes, respectively. The coagulating gland or anterior prostate is derived from two large buds per side, which grow cranially into the mesenchyme associated with the seminal vesicle [8]. In rats and mice, branching of the prostatic ducts primarily occurs postnatally. Branching patterns are unique for each lobe of the prostate. Buds of the ventral prostate extend into the mesenchyme of the UGS and undergo extensive dichotomous branching to give an 'elm tree' configuration [7]. By contrast, the ducts of the dorsal prostate initially elongate without branching. Subsequent ductal branching of dorsal prostatic ducts results in the generation of three to six terminal branches per main duct. Epithelial buds of the lateral lobe arise from the urethra with the dorsal group, but grow ventrally towards the ventral prostate. The ductal branching pattern of the lateral lobe resembles that of the ventral lobe [7]. Morphogenesis of new ductal branch points and ductal tips occurs as a result of locally elevated DNA

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synthesis at the tips. Sugimura et al. [9] have demonstrated that thymidine incorporation into DNA is 10- to 500-fold higher in ductal tips versus more proximal ductal regions of the mouse prostate.

In rats and mice, prostatic growth and ductal morphogenesis are essentially continuous processes that extend from late fetal life until adulthood. In contrast, normal human prostatic ductal morphogenesis and growth occurs in two separate periods, prenatally and pubertally [10, 11]. As in organs of the digestive [12–14], integumental [15], and urinary systems [16], the development of the prostate and other accessory sexual organs is dependent upon an interaction between epithelium and mesenchyme. However, a unique feature of prostatic development is its dependence upon androgenic stimulation. Thus, prostratic development provides a unique opportunity for examining the relationship between mesenchymal-epithelium interactions, androgen receptors, and androgenic effects as they pertain to the growth, morphogenesis, and function of the prostate.

Endocrinology of prostatic development

Growth and development of the prostate as well as the rest of the male internal genitalia are androgen dependent. Androgen production by the developing fetal testes is initiated before and continues throughout periods of prostatic morphogenesis [17–21]. Ablation of fetal testes during the ambisexual period of sex differentiation inhibits development of male accessory sex glands including the prostate [22, 23]. Similarly, chemical castration through administration of estrogens or antiandrogens suppresses development of the prostate and other male accessory sexual glands[24–29]. In organ culture, testosterone induces the female UGS to form prostatic buds and elicits their formation in the male UGS [6, 30–32]. During postnatal periods, prostatic development is also androgen dependent. Castration of newborn mice or rats greatly inhibits continued growth and development of the prostate, an effect that can be reversed by administration of testosterone [8, 33–34]. Administration of testosterone to immature males accelerates prostatic growth so that maximal prostatic size is attained precociously [35–36]. Once maximal prostatic size is achieved, further androgen treatment does not elicit further increase in DNA content [35]. These findings imply the existence of homeostatic mechanisms that are in some way linked to prostatic cell number.

While testosterone is the primary androgen produced by the fetal testis, DHT (dihydrotestosterone) appears to be the active intracellular androgen responsible for prostatic morphogenesis. DHT is produced by enzymatic reduction of testosterone by 5α-reductase. This enzyme has been detected in the UGS and external genitalia of rats, rabbits, and humans [20, 37–39]. Inhibitors of this enzyme feminize the external genitalia and urethra, and partially inhibit prostatic morphogenesis in the rat [40]. Humans with 5α-

reductase deficiency are born with female external genitalia; prostates are small or undetectable, but Wolffian derivatives are normal [41–43]. The development of a rudimentary prostate in the case of naturally occuring 5α-reductase deficiency or in the presence of 5α-reductase inhibitors suggests that the developing prostate may be responsive to exceedingly low levels of DHT or other androgens [40]. While androgen (particularly DHT) is an important factor in prostatic development, some aspects of neonatal prostatic growth may be independent of androgens. For example, castration of neonatal rats or mice does not completely inhibit development of the prostate [8, 33, 34].

Androgens act upon the developing UGS via specific androgen receptors, which have been detected both biochemically and autoradiographically [32, 44–47]. Autoradiographic studies in rodents have demonstrated that androgen receptors are expressed prenatally in the mesenchyme but not in the epithelium [44–47]. In the developing mouse prostate, epithelial androgen receptors appear initially at the end of the first week postpartum as the solid prostatic ducts are canalizing [45]. Males with the testicular feminization mutation (Tfm), in which androgen receptors are defective or absent, lack male secondary sex organs and have external genitalia that are feminized, even though their testes produced adequate amounts of testosterone. Tfm individuals develop a shortened vagina, a femal urethra, and female external genitalia; their Wolffian ducts (which normally form the epididymis, ductus deferens, and seminal vesicle) degenerate, and the prostate completely fails to develop [39, 48–50]. The Tfm syndrome occurs in the mouse, rat, human, and cow [39, 51, 52]. An analogous morphological phenotype can be elicited experimentally in certain species by administration of antiandrogens (competitive inhibitors that bind to androgen receptors) to pregnant females [24–26, 53].

Mesenchymal-epithelial interactions in prostatic development

Like all other organs containing an epithelial parenchyma, the development of the prostate is contingent upon an interaction between mesenchyme and epithelium. This interaction between urogenital sinus mesenchyme and epithelium (UGM and UGE, respectively) leads to prostatic development when androgens are present and to vaginal development when androgens are absent. During prostatic development the mesenchyme induces epithelial ductal morphogenesis and differentiation.

Urogenital sinus mesenchyme can function both as a permissive and an instructive inductor. Tissue interactions characterized as permissive inductions are those in which mesenchyme allows the epithelium to express its normal developmental fate. Instructive inductions are those in which mesenchyme induces in epithelium to express an entirely new developmental fate determined by the mesenchyme itself. Table 1 shows a series of tissue

Table 1. Instructive and permissive tissue interactions in recombinants prepared with urogenital and non urogenital tissues

Mesenchyme	Epithelium	Germ layer of epithelial origin	Result	Type	Reference
UGM	UGE	Endoderm	Prostate	Permissive	Cunha [54]
UGM	SVE	Mesoderm	Seminal vesicle	Permissive	Cunha [54]
SVM	UGE	Endoderm	Prostate	Permissive	Cunha [54]
SVM	SVE	Mesoderm	Seminal vesicle	Permissive	Cunha [54]
UGM	Preputial gland	Ectoderm	Preputial gland	Permissive	Cunha [55]
UGM	Salivary gland	Ectoderm	Salivary gland	Permissive	Cunha [56]
SVM	Preputial gland	Ectoderm	Preputial gland	Permissive	Cunha [55]
SVM	Salivary gland	Ectoderm	Salivary gland	Permissive	Cunha [56]
UGM	Esophagus	Endoderm	Esophagus	Permissive	Cunha, unpublished
UGM	Prostate	Endoderm	Prostate	Permissive	Norman *et al.* [57] Neubauer *et al.* [58]
UGM	Epidermis	Ectoderm	Skin	Permissive	Cunha [55]
UGM	Bladder	Endoderm	Prostate	Instructive	Cunha *et al.* [59, 60]
UGM	Vagina	Endoderm/mesoderm	Prostate	Instructive	Cunha [61]

recombinants of both the permissive and instructive types. It is thought that expression of the normal epithelial prospective fate (permissive induction) is due to prior irreversible commitment or determination of epithelial differentiation by inductive process occurring at earlier developmental periods. Of course, implied in any inductive process is the idea that the inductive influence of the mesenchyme must be compatible with the expression of the epithelial phenotype. To elucidate these points, the interaction between UGM and seminal vesicle epithelium (SVE) will be discussed. UGM + SVE recombinants differentiate as seminal vesicle. Seminal vesicle epithelium is derived from the lower end of the mesodermally derived Wolffian duct, whose developmental repertoire includes the formation of epididymis, ductus deferens, and seminal vesicle, but not prostate [62, 63]. Therefore, as a result of prior inductive interactions, the prospective SVE has been determined to form seminal vesicle and displays its glandular option (seminal vesicle) when associated with a glandular inductor such as homologus seminal vesicle mesenchyme (SVM) or heterologous UGM [54]. In association with other mesenchymes that are either derived from nonglandular organs or organs whose development is not dependent upon androgens, seminal vesicle development fails [55, 56]. Thus, the expression of seminal vesicle differentiation in prospective SVE appears to occur 1) because the prospective SVE was irreversibly committed to the seminal vesicle pathway, 2) because the SVE was associated with an appropriate glandular inductor (SVM or UGM), and 3) because the mesenchyme (UGM or SVM) is an androgen target tissue capable of functioning as a mediator of androgenic effects (see below).

By contrast, in instructive inductions the epithelium is not stabily committed and, therefore, retains the ability to respond to a heterologous mesenchymal inductor. For example, in the presence of androgens, UGM can induce prostatic development in epithelia of the urogenital sinus, postnatal vagina, and fetal or adult urinary bladder [59–61, 64]. It should be stressed that all of these epithelia are derived in total or part from the embryonic urogenital sinus [62, 63]. Extensive analysis of UGM + adult bladder epithelium (BLE) tissue recombinants shows that the epithelial ducts induced by UGM express histological, ultrastructural, and functional features indicative of prostate: androgen receptors, prostate-specific antigens, androgen dependency for DNA synthesis, prostatic patterns of protein synthesis when assessed by two-dimensional gel electrophoresis, and histochemical profiles indicative of the prostatic phenotype [59, 60, 65, 66]. None of these changes occur if the epithelium is grown by itself [60, 67].

Both instructive and permissive inductions by UGM appear to be mediated by similar, if not identical, signals in several mammalian species. For this reason prostatic differentiation occurs in either UGM + UGE or UGM + BLE recombinants prepared with epithelium and mesenchyme from two different species. Such heterospecific recombinants have been prepared with mouse, rat, rabbit, and human tissues [68]. From these findings it is evident that the mediators of these inductive interactions are highly conserved in different mammalian species.

Under the influence of androgens, prostate develops from the ambisexual UGS, whether it is derived from either male or female fetuses. However, the ability of the female UGS to form prostate is under strict temporal constraint. Injection of testosterone into pregnant females results in the induction of prostatic development in the urogenital sinus of female fetuses [69]. Similarly, culture of the female urogenital sinus in the presence of testosterone induces the development of prostatic buds [31, 32]. Urogenital sinuses from female fetuses and vaginae derived from newborn mice (<5-day-old) form prostate when grafted to intact adult male hosts [61]. Thus, the ability of the female urogenital sinus to give rise to prostate in response to androgens is temporally constrained to early development periods [61]. Since the development of new ductal architecture in the developing prostate also requires an inductive mesenchyme as well as a responsive epithelium, tissue interactions were studied as a possible explanation for this loss of responsiveness. The loss of the ability of the female urogenital sinus to form prostate in response to androgens is due to maturational changes within the mesenchyme. Vaginal stroma derived from newborn mice can function as a prostatic inductor when associated with epithelium from either the fetal urogenital sinus [61] or urinary bladder [Cunha, unpublished]. However, this ability to function as a prostatic inductor is progressively lost when the vaginal stroma is derived from older donors. In contrast, vaginal epithelium from donors 1- to 20-days-old remained able to form prostate when grown in association with embryonic UGM [61]. Thus, the ability of the female urogenital sinus and the sinus vagina (that portion of the vagina derived from the urogenital sinus) to form prostate is dependent on the expression of the inductive activity of its mesenchyme. While it is not possible to elucidate epithelial responsiveness or unresponsiveness to a mesenchymal inductor in biochemical or molecular terms, developmental history clearly plays an important role.

The primitive endodermal urogenital sinus, which is derived from the ventral portion of the cloaca, forms the epithelial lining of a multitude of structures in both males and females, many of which develop a sensitivity and dependence upon sex steroids, while other structures (bladder and perhaps certain regions of the urethra) do not [62, 63]. This common embryonic derivation from hindgut endoderm appears to be essential for epithelial responsiveness to prostatic inductors in that only epithelia derived from the endodermal urogenital sinus have been induced to express prostatic differentiation (Table 1). Responsiveness to prostatic induction is not a quality common to endoderm per se because epithelium from the adult esophagus (foregut endoderm) does not form prostate when combined with UGM [Cunha, unpublished]. Moreover, several fetal epithelia of ectodermal origin (back skin, plantar skin, snout skin, mammary gland, preputial gland, and salivary gland) also do not form prostate when grown in association with UGM [54–56] [Cunha, unpublished]. Therefore, epithelial responsiveness to prostatic induction may itself be a unique property of endoderm of the urogenital sinus.

The role of the epithelial:stromal ratio in prostatic growth

Prostatic epithelial growth is dependent on factors extrinsic and intrinsic to the prostate. Testosterone and its metabolites (produced outside of and within the prostate) are necessary extrinsic factors since net prostatic growth does not occur in a state of androgen deprivation. However, factors other than androgens are also important in regulating prostatic DNA synthesis, since the prostate ceases growth in adulthood as mature organ size is attained, even though androgen levels continue to remain high. Likewise, exogenous androgens cannot cause overgrowth of the adult rodent prostate [35]. Indeed, in intact adults androgen levels are high while prostatic epithelial cell proliferation is low and in equilibrium with cell death [70–72]. The importance of intrinsic factors in prostatic growth is underscored by the following experiment. When prostatic ducts obtained from an intact adult male mouse were grafted under the kidney capsule of an intact male host, the graft was maintained but did not grow [57]. However, when a fetal urogenital sinus (prostatic analgen) or a neonatal prostatic rudiment was grafted as above, they each formed an entire prostate [54, 61, 73, Cunha, unpublished]. Thus, prostatic ducts from sexually mature intact males do not grow in response to androgen levels present in intact males, whereas embryonic or neonatal prostatic rudiments are capable of growing under similar conditions. How can this paradox be explained? The significance of the epithelial:stromal ratio may provide clues.

Based upon analyses of random tissue sections, DeKlerk and Coffey [74] demonstrated that castration evoked a disproportionate loss of epithelial versus stromal cells, which changed the epithelial:stromal ratio by a factor of 10 (4.54 to 0.43). Sugimura et al. [75] reported that during prostatic regression the epithelial cells of the ductal tips almost completely degenerate and that stromal tissue, which could not be discerned distinctly in whole-mount preparations before regression, became visible. This raises the distinct possibility that the relative loss of epithelial and stromal cells following castration may be unequal in different regions of the gland, as suggested by English et al. [76]. This change in the epithelial:stromal ratio may have important consequences in the regulation of prostatic epithelial growth, both during prostatic regeneration in castrates subsequent to androgen replacement therapy and during prepubertal prostatic development as described below. When prostatic development is begun in the fetus, small epithelial prostatic buds invade the large mass of mesenchyme surrounding the endodermal urogenital sinus. This is a stage during which growth potential is at its highest since the small embryonic rudiment has the potential to form a complete adult organ. At this stage of prostatic development, the epithelial: mesenchymal ratio greatly favors the mesenchyme. This observation is by no means unique to the prostate. Other organs such as the lung and seminal vesicle and the salivary, bulbourethral, preputial, and mammary glands exhibit comparable early organogenetic stages in which the epithelial com-

ponent is a minute, unbranched bulbous or tubular rudiment surrounded by a substantial mass of mesenchyme [8, 54, 77–82]. Thus, for many organ rudiments maximal growth potential of the parenchyma is present when the amount of mesenchyme vastly exceeds the amount of epithelium.

During prostatic development the epithelial ducts elongate and arborize within the mesenchyme [7]. With time the mesenchyme becomes filled by invading, branching epithelial ducts. As this occurs, the stromal tissue becomes progressively more difficult to perceive in whole-mounts as it becomes organized into the investing sheaths of smooth muscle and connective tissue cells that encircle the epithelial ducts. Equivalent processes occur in the development of other structures such as the lung, and the salivary and bulbourethral glands. Thus, during postnatal development the rat prostate changes from a predominantly mesenchymal to a primarily parenchymal organ with an epithelial:stromal ratio of about 5:1 [74]. Similarly, during development of the baboon prostate, the ratio of epithelium:stroma is 1:4 in the neonate but switches to about 3:4 following puberty. While there is an increase in the amount of both epithelium and stroma during the pubertal growth spurt in the baboon, the increase in the stromal population precedes the increase in the epithelial population [83].

Studies on development of the prostate emphasize the importance of epithelial:mesenchymal ratios in determining final organ size. Chung and Cunha [73] dissociated urogenital sinuses into UGE and UGM. Homotypic UGM + UGE recombinants were prepared in which the UGM was held constant at 1X (the amount of epithelium or mesenchyme obtained from a 16-day urogenital sinus while the amount of UGE was varied from 1X to 0.01X. Conversely, another set of tissue recombinants was prepared in which the UGM was varied from 0.1X to 2X keeping the UGE constant at 1X. All recombinants were grown for 1 month in intact male hosts, and then wet weight and DNA content were measured. The results showed that reduction in the initial amount of UGE combined with 1X UGM did not influence the final prostatic mass attained by the recombinants [73]. Conversely, when the amount of UGE was held constant (1X) and the amount of UGM varied, final tissue mass increased in proportion to the amount of UGM utilized. These findings suggest that the amount of mesenchyme determines final organ size, which may be relevant to the regulation of prostatic growth in castrated adult males.

Since growth of the prostatic rudiment to the adult size is associated with a marked shift in the epithelial:stromal ratio (see above), it may be that growth responsiveness of the adult prostate following androgen replacement therapy necessitates that the epithelial:stromal ratio favors the stromal elements before growth can be induced. This would explain the inability of the prostate to be induced to grow beyond normal adult size by administration of hyperphysiologic doses of androgen to intact males and the requirement for 4–7 days of androgen deprivation before testosterone can stimulate DNA synthesis (see above). This concept has been recently tested with adult pro-

static ducts by experimentally varying the ratio of prostatic epithelium to mesenchyme in tissue recombinants. Segments of prostatic ducts (PR) containing about 1500 epithelial cells from intact adult mice were grafted either by themselves or in combination with UGM or bladder mesenchyme. Individual ducts were maintained but did not develop when grafted by themselves or when recombined with bladder mesenchyme. However, when associated with UGM (UGM + PR recombinants), the ductal tip produced 30–35 mg (wet weight) of prostatic tissue containing hundreds of prostatic ducts following 1 month of growth in adult male hosts [57]. This phenomenal growth occurred in ducts from intact donors, and, therefore, the ducts did not require prior castration-induced atrophy or cell loss as a condition for growth response, as suggested earlier by Bruchovsky et al. [84]. Through analysis of tissue recombinants composed of a prostatic ductal tip with 1X to 8X UGM, Neubauer et al. [58] have shown that new prostatic ductal tissue is formed in proportion to the amount of UGM utilized. Also consistent with these findings are the studies of Chung and colleagues [85, 86], which have shown an increase in prostatic growth in situ when UGM or an intact urogenital sinus was grafted directly into the prostate of intact mature males. However, in the experiments described above, it should be noted that the huge increase in prostatic epithelium occurs when the adult prostatic epithelium is experimentally recombined with fetal UGM. Comparable experiments using adult prostatic stroma have not as yet been performed. Due to difficulties in isolating prostatic epithelium and stroma in adults, it is unknown whether associating an excess of adult prostatic stromal cells with prostatic epithelium would elicit epithelial proliferation. However, in the mammary gland, stroma from both the fetus and adult are interchangeable in that they both stimulate the growth and branching morphogenesis of either fetal or adult mammary epithelium [87–91]. All of these studies stress the importance of mesenchymal-epithelial interactions in regulating epithelial growth within developing and mature hormonally responsive glands.

Mesenchyme as a mediator of androgenic effects upon epithelium

While the androgen dependency of prostatic development has been known for some time [6, 92], androgen dependency now can be related to mesenchymal-epithelial interactions through analysis of tissue recombination experiments utilizing Tfm mice. These mice are insensitive to androgens due to defective androgen receptors and thus fail to form prostates [48]. The four possible types of tissue recombinants constructed between Tfm and wild-type UGS were exposed to physiological levels of androgens as a result of grafting the recombinants into intact male hosts. Prostatic morphogenesis occurred only in those recombinants prepared with wild-type mesenchyme. The genotype of the epithelium was irrelevant as both wild-type and Tfm epithelia developed prostate in association with wild-type UGM. In contrast, prostatic

differentiation failed to occur in recombinants constructed with Tfm mesenchyme [64, 65, 93], even when wild-type epithelium was used. In similar experiments with the embryonic mouse mammary gland [94, 95], it has been shown that androgen-induced epithelial regression requires an androgen-responsive (wild-type) mesenchyme. Thus, in the developing prostate and embryonic mouse mammary gland, mesenchyme is the actual target and mediator of androgenic effects upon the epithelium. This concept is corroborated by the observation of nuclear ^{3}H-DHT bindings sites in mesenchymal cells of wild-type UGS and mammary gland using steroid autoradiography [44–47]. Tfm UGM lacks nuclear ^{3}HDHT bindings sites [Cunha, unpublished].

The development of prostate in tissue recombinants composed of wild-type UGM associated with either Tfm UGE or Tfm bladder epithelium (BLE) involved three major processes: ductal morphogenesis (the formation of a branched network of epithelial ducts), epithelial proliferation, and secretory cytodifferentiation. All of these processes are androgen dependent and are expressed in the Tfm epithelium, which remains androgen-receptor negative even after prostatic induction [96, 97]. This demonstrates that these androgen-induced events must be regulated by the androgen-receptor-positive stromal cells [96–98].

Since the initial analyses of the so-called Tfm/wild-type model system focused upon developmental events involved in prostatic organogenesis, it could be argued that these conclusions might not be relevant to the mature prostate. For that reason, wild-type [UGM + Tfm BLE recombinants have been grown to maturity and compared with wild-type prostate or tissue recombinants composed of wild-type UGM + wild-type BLE, which also form prostate whose epithelial cells express androgen receptors [66, 99]. Proteins produced by wild-type UGM + Tfm BLE recombinants are remarkably similar, as judged by two-dimensional electrophoresis, but do show some minor differences in comparison to the wild-type prostate [100]. Prostatic epithelial cells of wild-type UGM + Tfm BLE and wild-type UGM + wild-type BLE recombinants express similar regressive changes, as judged histologically in response to androgen deprivation [98, 100].

Androgen-induced DNA synthesis, as judged by both biochemical and autoradiographic procedures, is comparable in prostates that are either completely wild-type or are composed of wild-type mesenchyme and Tfm epithelium [98, 100]. Thus, several lines of evidence support the concept that many aspects of epithelial differentiation are regulated by androgens indirectly through androgen-dependent mediators of stromal origin. This concept, suggested initially by Franks and Barton [101], Fransk et al. [102], and Cunha [54, 56, 67], is further strengthened by several lines of circumstantial evidence. Numerous reports show that testosterone is not mitogenic for cultured prostatic cells in vitro [102–105]. In contrast, in organ cultures of the prostate in which the epithelial-stromal interaction is preserved, epithelial DNA synthesis is stimulated by addition of testosterone to the medium [106–111]. These data taken together have generated considerable

interest in the role of stroma in prostatic growth and physiology. The role of epithelial androgen receptors is yet to be defined.

Tissue interactions in carcinogenesis

The ability of prostatic epithelium to respond to a prostatic inductor is expressed at all ages from fetal to adult, since prostatic ductal morphogenesis can be induced by UGM in UGE as well as in adult prostatic epithelium as described above [54, 57, 58, 67]. Androgen-induced regeneration of the prostate in castrated males is another example of morphogenetic processes in the adult prostate. Since stromal-epithelial interactions are operative in the adult prostate and in several other adult hormone target organs [57, 89, 90, 91, 112], such interactions may play a role in abnormal epithelial differentiation and in carcinogenesis. Evidence for this in the case of the prostate is derived from studies in which nonglandular transitional cell carcinomas (bladder tumors) have been induced by UGM to undergo adenocarcinomatous (glandular) differentiation, thus resembling prostatic adenocarcinomas [113]. Other studies stress the importance of stromal-epithelial interactions in breast, bladder, and epidermal carcinogenesis [114–120].

Benign prostatic hyperplasia (BPH), in which new ductal-acinar architecture is laid down in prostates of aged men [11, 121] can also be considered a developmental phenomenon whose etiology may be related to stromal-epithelial interactions. In this regard, McNeal [121–122] has proposed that the pathogenesis of BPH is due to the reexpression of embryonic inductive activity within the stromal cells of BPH nodules. McNeal has proposed that BPH stroma induces ductal arborization in nearby prostatic ducts, thereby directing the growth of new ducts towards the center of the inductive nodule. Consistent with McNeal's hypothesis is the discovery that the proportion of stromal tissue is elevated in BPH [123, 124].

Concluding remarks

Future studies on the mechanism of interactions between epithelium and stroma are going to provide important new insights into the cellular processes regulating the development, growth, and function of the prostate. By the same token, future progress on the mechanism of normal prostatic growth and development will surely have application to BPH and prostatic adenocarcinoma, and may ultimately lead to therapeutic approaches based upon a new conceptual framework, the stromal-epithelial interaction.

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10. Biological basis for chemohormonal therapy for prostatic cancer

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Introduction

Since the pioneering studies of Charles Huggins in the 1940s, androgen ablation therapy has been the standard treatment for metastatic prostatic cancer. This is because nearly all men with metastatic prostatic cancer have an initial, often dramatic, beneficial response to this hormonal therapy. This initial response demonstrates that at least a portion of the cancer cells are androgen responsive. While this initial response is of substantial palliative value, unfortunately, essentially all treated patients eventually relapse to an androgen-insensitive state and succumb to the progression of their cancer; cures, if any, are rare [1]. Because of this nearly universal relapse phenomenon, the annual death rate from prostatic cancer has not decreased at all over the subsequent 40 years since hormonal therapy became standard therapy [2]. In fact, over the last 40 years, the superficially benign nature of androgen ablation therapy has tended to disguise the fact that prostatic cancer is still a fatal disease for which no effective therapy is presently available [3]. This does not mean that hormonal therapy is not useful in the treatment of metastatic prostatic cancer, only that such hormonal therapy will have been used in combination with additional forms of therapy if the cure rate for metastatic prostatic cancer is ever going to be substantially increased.

In order to develop new and more effective forms of therapy for the treatment of metastatic prostatic cancer, an understanding of the basic mechanism involved in the relapse phenomenon, wherein an initially responsive prostatic cancer progresses following androgen ablation therapy to an androgen-resistant state, is critically required. The answer to this question is fundamental since, depending on the mechanism, the optimal approach to curative therapy will be quite different. There have been at least three distinct mechanisms proposed for the relapse of prostatic cancer to standard androgen ablation therapy. These three distinct mechanisms propose that relapse is due to either: 1) inadequate elimination of androgen produced by standard androgen ablation, 2) adaptation of initial androgen-dependent prostatic cancer cells to become androgen-independent due to the low androgen environment produced by androgen ablation (enviromental adaptation model),

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or 3) clonal selection of androgen-independent prostatic cancer cells heterogeneously present within the prostatic cancer before therapy is begun (environmental selection model). Each of these three mechanisms will be analyzed as to their validity based upon the presently available data.

Inadequate androgen suppression model

This mechanism proposes that prostatic cancers are homogeneously composed of androgen-dependent cancer cells that, however, can vary widely with regard to the absolute concentration of androgens needed to stimulate their proliferation and prevent their death [4]. The standard forms of androgen ablation presently used (i.e., surgical or medical castration) eliminate testicular androgen but do not eliminate adrenal androgens. Thus, it has been proposed that the standard forms of androgen ablation are only partial, not complete, androgen ablation [5]. If some of the cancer cells within a prostatic cancer can respond to any level of androgen stimulation (i.e., any concentration of androgen will allow some of the cancer cells to continue to grow), then the complete elimination of all serum and prostatic androgen would be absolutely required in order to kill all the cancer cells. If this concept is correct, then the presently used forms of partial androgen withdrawal would not be optimal [6].

While these standard therapies do eliminate testicular androgen, adrenal androgens are not eliminated [7, 8]. Thus in the human male, as in the rat, castration reduces DHT in the cancer cells by greater than 80%, but it does not completely estimate all androgens [7–10]. The adrenals in males of both rats [10] and humans [7, 8] thus supply 10–20% of the prostatic DHT. It has been postulated that a more complete form of androgen ablation could be achieved by combining a direct-acting antiandrogen, to block any possible effects of andrenal androgen, with surgical or medical castration to eliminate the testicular androgens. Such a combinational approach theoretically could be more effective in the treatment of prostatic cancer than castration alone, if indeed the 10–20% of the DHT remaining in prostatic cancer cells could be shown to have a stimulatory effect on the proliferation of these cancer cells.

When a biological response is a direct result of a single reversible interaction between a ligand and its receptor (e.g., substrate-enzyme interaction, antigen-antibody reaction, etc.), the process characteristically obeys a simple continuous dose-response relationship [12]. If the total concentration of receptors remains constant, the magnitude of the biologicasl response should increase as a continuous hyperbolic function of the ligand concentration [12]. Under these conditions, the magnitude of biological response is continuously proportional to the concentration of the ligand from zero concentration up to the point of saturation occupancy of the receptor. At any ligand concentration, there will be always some graded response produced.

In direct contrast to the simple situation in which the biological response occurs as a continuous graded process, when a biological response occurs as an all-or-none quantal process (e.g., pregnancy, death, etc.), then the shape of the dose-response curve is not a continuous hyperbola, but is instead a discontinuous asymmetrical sigmoidal function of ligand concentration [13–15]. Such a discontinuous, sigmoidal shape, dose-response curve is characteristic of an all-or-none quantal process and is due to the fact that there is a critical threshold concentration of ligand below which no biological response is evoked. This is because for a quantal process, the biological response occurs only when a critical concentration of ligand has interacted with its receptor to produce a sufficiently large biochemical change to overcome some type of threshold condition [13–15]. For example, the contraction of the muscle fibers takes place as an all-or-none quantal process and begins to occur only when a critical concentration of acetylcholine is present that can increase the end-plate potential to a sufficient threshold value. The shape of the dose-response curve (i.e., continuous hyperbolic versus discontinuous sigmoidal), therefore, can be used to determine if a biological process occurs as a continuously graded or a quantal process.

Within the prostate, androgen action is initiated by conversion of various androgens, predominantly testosterone, into dihydrotestosterone (DHT). Dihydrotestosterone, by virtue of its preferential retention by androgen receptors in the nuclei of prostatic cells, appears to be the functional intracellular androgen [16–18]. Therefore, the shape (i.e., continuous hyperbolic or a discontinuous sigmoidal) of the prostatic DHT content (dose) versus prostatic cell number (response) curve can be used to determine if the androgen-induced increase in prostatic cell number occurs as a continuously graded process increasing with any level of prostatic DHT or whether the process is quantal, occurring only when a critical threshold of prostatic DHT is reached. In order to make this distinction, the dose-response curve must be performed from zero level of prostatic DHT up to some saturating amount of DHT.

In the previous studies examining the relationship between DHT and prostatic cell number, the lowest value for prostatic DHT and prostatic cell number have been obtained by using castrated rats [9, 11, 18, 19]. Recent studies have demonstrated that in order to deplete the prostatic DHT to undetectable levels in the rat, however, animals must be both castrated and adrenalectomized [10]. In rats only castrated, the serum level of testosterone is not completely eliminated (i.e., 4% of intact value remains) and thus in long-term castrated rats the prostatic DHT content is still approximately 10–20% of that of intact rats [10, 11]. Treatment of castrated rats with testosterone-filled Silastic implants of varying diameters and lengths allows the serum testosterone levels, and thus the prostatic DHT levels, to be varied over a wide range of values. Therefore, by using castrated-adrenalectomized rats, castrated rats given no treatment, and castrated rats given testosterone-filled Silastic implants of varying lengths, it is possible to study the prostatic

DHT content (dose) versus total prostatic cell number (response) relationship ranging from undetectable to pharmacologically large levels of prostatic DHT. Only in this way is it possible to determine if the prostatic DHT versus prostatic cell number response curve characteristically has a continuous hyperbolic or a discontinuous sigmoidal shape.

Such dose-response studies have demonstrated that the shape of the prostatic DHT content dose versus cell number response curve is not continuously hyperbolic, but is instead discontinuously sigmoidal [20]. This demonstrates that an androgen-induced increase in prostatic cell number occurs as a quantal process, which can only begin to occur when the concentration of prostatic DHT is above a critical threshold value (i.e., 1.0 ng/10^8 cells for the rat ventral prostate). Thus, in order to completely prevent this androgenic stimulation of prostatic cell number, prostatic DHT has to be lowered to below this critical threshold level but does not have to be completely eliminated. In addition, since prostatic DHT is itself derived from serum androgen, predominantly testosterone, this means that in order to completely prevent all the androgenic stimulation of prostatic cell number, the serum concentration of androgen must be lowered to below a critical threshold value (<0.60 ng/ml but >0.25 ng/ml of testosterone in the rat) but does not have to be completely eliminated.

In addition to the present animal studies, Oesterling et al. have demonstrated that the small levels of androgens produced by human adrenals do not have a significant stimulatory effect on human prostate and are not capable by themselves of supporting prostatic growth [21]. These human data suggest that, like the situation for the rat, the stimulation of human prostatic cells by androgen follows a quantal dose-response relationship, and thus there is a critical threshold level of DHT below which no growth response is evoked.

This critical threshold level of prostatic DHT appears to be higher than the levels of DHT obtained following castration alone in both rat and man. That the level of cellular DHT is adequately depressed to this critical threshold value by castration alone is supported by a series of animal and human studies [9, 19, 22–26]. Indeed, in animal studies using a series of transplantable androgen-responsive Dunning rat prostatic cancer sublines, it has been demonstrated that combining antiandrogen with castration has no additional effect upon survival than that produced by castration alone [9]. In addition, it has demonstrated that it is even possible to raise the serum testosterone level slightly above that observed in castrated rats (i.e., increase from 0.1 ng/ml to 0.25 ng/ml) without increasing the growth of the prostatic cancer and thus descreasing the survival of the tumor-bearing host [9, 19]. Such an observation is only compatible with the growth of androgen-responsive prostatic cancer being a quantal, not a continuous graded, process stimulated by androgens. This may explain why a series of human clinical trials have failed to demonstrate any statistically significant increase in host survival when antiandrogens are combined with castration [23–26].

In addition, if all the cells in a prostatic cancer were androgen dependent

but they varied widely with regard to the absolute concentration of androgens needed to stimulate their growth, then it should be possible to castrate a man and eliminate all of the cancer cells dependent upon higher levels of androgen and then later, at relapse, either remove or block the adrenal androgens to completely eliminate all the remaining highly sensitive cancer cells. If this model were correct, it predicts that theoretically all men treated initially with partial androgen ablation and who subsequently relapse, should all respond to secondary forms of androgen ablaton targeted at eliminating or blocking the andrenal androgens. Clinically, it is well established, however, that only a very small population (>10%) of men treated with secondary forms of androgen ablation at relapse respond with an objective response [27].

These results are completely incompatible with the concept that insufficient androgen suppression is the major mechanism for relapse of prostatic cancer to testicular androgen withdrawal. Thus, the scientific basis for complete androgen withdrawal as the only acceptable form of androgen ablation [28–30] does not appear supportable based upon the scientific facts.

Enviromental adaptation versus environmental selection model

One way in which the relapse to androgen withdrawal can occur is that prostatic cancers initially could be composed of tumor cells that are homogeneous, at least in regard to their dependence on androgenic stimulation for their maintenance and continuous growth (i.e., androgen-dependent cancer cells). Following castration, most of these dependent cells stop proliferating and die, thus producing an initial positive response to withdrawal therapy. Some of these androgen-dependent cells, however, under environmental pressure, could randomly adapt to become androgen independent. These androgen-independent cells, once formed, proliferate without the requirement for androgenic stimulation and thus repopulate the tumor, producing a relapse after castration. In such an explanation, the changing host environmental conditions following castration are assumed to be critically involved in inducing the adaptive transformation of initially androgen-dependent to androgen-independent tumor cells. This process is therefore called the *environmental adaptation model.* In contrast to this environmental adaptation model, where the changing androgen environment following castration is assumed to play a direct inductive role, an alternative explanation is possible in which the role played by the changing androgen environment following castration is only indirect. It is possible that initially prostatic cancers are heterogeneous, being composed of preexisting clones of androgen-dependent and androgen-independent tumor cells. The androgen-independent cancer cells can be of two types: cells that are neither dependent on nor sensitive to androgeneic stimulation for their growth (i.e., androgen-independent insensitive cells) or cells that grow faster in the presence of adequate andro-

gen levels but that can still grow continuously, even when no androgen is present (i.e., androgen-independent sensitive cancer cells) (for examples of both of these types of androgen-independent cells see reference 31). Regardless of what type of androgen-independent cells (i.e., insensitive or sensitive) are present, castration, in such a context, would result in the death of only the androgen-dependent cells without stopping the continuous growth of the androgen-independent ones. While this would produce an initial positive response, these independent cells would continue to proliferate following castration. Even if these androgen-independent cells initially represented only a small fraction of the starting tumor, their continuous growth would eventually not only completely replace any tumor loss due to the death of the androgen-dependent cells, but it would progressively reexpand the tumor, producing a relapse.

Regardless of whether environmental adaptation or selection is the mechanism for relapse to androgen withdrawal therapy, eventually clones of androgen-independent prostatic cancer cells grow to kill the patient. Therefore, of what clinical importance is the resolution of the question of which of the two possible mechanisms is actually responsible for relapse? The importance of resolving whether adaptation versus clonal selection is the mechanism responsible for relapse is that the optimal therapy for prostatic cancer is very different depending upon the answer.

The environmental adaptation model: The case for a more complete androgen withdrawal

If the environmental adaptation model is the mechanism for the relapse to standard androgen ablation therapy, then it is possible that the presently utilized forms of androgen ablation may not be ideal for the treatment of prostatic cancer. This is because while the standard forms of surgical or chemically induced castration do lower the serum testosterone level by over 90%, they do not completely eliminate all potential serum androgens. Since low levels of nongonadal (e.g., adrenal) androgens are left following castration, this treatment induces a partial, not a complete, androgen withdrawal. This has led some investigators to suggest that a more complete form of androgen withdrawal in which the very low levels of nontesticular serum androgen remaining following castration are neutralized by simultaneous treatment with a direct-acting antiandrogen might be more effective than simply castration alone [5, 32]. In particular, Labrie et al. [5] have used a combination of a luteinizing hormone releasing hormone (LHRH) analog plus an antiandrogen to produce what they term 'a complete androgen withdrawal.' The rationale for such a combination approach is based upon Dr. Labrie's premise that 'all or nearly all tumoral prostatic cells are androgen dependent at the beginning of the disease and that loss of androgen dependence occurs by genetic loss this property during cell divisions ... it appears logical to

propose the initiation of this (complete androgen withdrawal treatment) as early as possible after diagnosis to minimize the appearance of androgen-insensitive cancer cell clones' [5]. In addition, Labrie asserts that '99% of prostatic tumors, even at the stage of metastases, are still androgen sensitive. Instead of being present at the beginning of treatment, most androgen-insensitive cells develop when tumor cells are exposed to the low androgen milieu provided by the adrenal androgens' [6]. Since once these androgen-independent prostatic cancer cells develop, the patients become incurable by any type of hormonal therapy, Labrie has postulated that by combining antiandrogen with castration (either surgical or chemical), it might be possible to kill all of the androgen-dependent prostatic cancer cells before they can progress to become androgen-independent cancer cells.

Labrie's group termed such a combination of surgical a medical orchiectomy with the addition administration of the antiandrogen flutamide *complete androgen blockade* and have reported preliminary studies using this form of hormonal therapy [28–30]. While these investigators interpret their preliminary data as suggesting improvement in response and survival, the short follow-up time for their study and their patient selection and evaluation criteria appears to influence their conclusions. Although the number of patients has continued to increase since their initial reports, the average follow-up time (i.e., 1.4 years) has remained constant in their later studies. Nevertheless, the projected response and survival rate have decreased continuously over the last years. For example, the projected 2-year response rate decreased from 81% in their 1985 report (calculated on 87 patients) [29] to 60% in their 1986 report (calculated on 119 patients) [30]. Therefore the question remains as to how much further the response and survival rates will decrease when the patients in the study of Labrie et al. have been followed for a longer period of time, so that actual rates are obtained rather than projected.

In addition, there are other major limitations to the Labrie study. First, the study is a nonrandomized clinical trial; no partial androgen withdrawal group was randomized and followed prospectively in parallel over the same time interval with the complete androgen withdrawal group. Second, the trial was not a double-blind study (i.e., the evaluating physician knew the treatment the patient received). These last two points are critical since in other clinical trials, more complete androgen withdrawal therapy has not been shown to be any more effective than castration alone. For example, Beland et al. [23] performed a randomized double-blind clinical trial comparing the effectiveness of surgical castration with or without simultaneous treatment with the antiandrogen, Anadron, on previously untreated men with metastatic prostatic cancer. In this study, the evaluating physician did not know which patients were or were not receiving the antiandrogen or placebo. This randomized, double-blind study could not demonstrate any statistically significant increase in survival between castrated patients treated with or without antiandrogen.

Likewise, Schroeder et al. [24], in a randomized clinical trial of previously

untreated D_2 prostatic cancer patients, demonstrated that androgen withdrawal consisting of the daily LHRH analog plus cyproterone acetate was no more effective in preventing progression of the cancer than was LHRH analog alone (i.e., 39% of patients progressed within 12 months on the combinational treatment group versus 38% progression in the LHRH alone group). In addition, similar negative results have been reported by Zabra et al. [25] using the nonsteroidal antiandrogen, Anandron. In this clinical trial, previously untreated D_2 prostatic cancer patients were randomized to receive either 1) castration alone, 2) castration plus simultaneous Anandron, or 3) LHRH plus simultaneous Anandron. All patients were followed for 14–19, months. The progression rate for the castration alone group was 30%, for the castration + Anandron group was 50%, and for the LHRH + Anandron group was 36%. In addition to these negative clinical trials in humans, animal studies, using well-characterized, serially transplantable rat prostatic cancers, have also failed to demonstrate any additional effect of combining an antiandrogen, be it either cyproterone acetate or flutamide, with surgical or medical castration [9, 22].

The environmental selection model: The case for combining androgen withdrawal and chemotherapy and/or radiation

There are several major clinical observations that do support the critical assumption upon which the complete androgen withdrawal theory is based. First, while the adrenals do supply steroids to the blood that theoretically could act as androgens, no one has actually demonstrated that in humans these adrenal androgen precursors in fact have major effects upon prostatic cell growth. Indeed, a recent study by Oesterling et al. [21] demonstrates that the adrenal glands do not have a significant simulatory effect on the human prostate and are not capable by themselves of supporting prostatic growth. This conclusion is based upon the following findings. In patients with panhypopituitarism, in whom there is no testicular nor adrenal function, the prostates are completely atrophic by both histological and morphological criteria, thus demonstrating a complete lack of androgenic stimulation. When these atrophic prostates were compared to those of patients with normal adrenal function but no testicular function (hypogonadotropic hypogonadism or prepubertal castration), no difference was found in their degree of atrophic morphology or histology, demonstrating that adrenal function alone does not have a stimulatory effect on the human prostate and is not capable of supporting prostatic growth.

Second, prostatic cancers, when they become clinically manifest, are rarely phenotypically homogeneous with regard to the clones of cancer cells comprising individual tumors. For example, Kastendieck [33] demonstrated that of 180 clinically manifest prostatic cancers removed surgically from previously hormonally untreated patients, 60% of these cancers were already histo-

logically heterogeneous, being composed of a mixture of several different cancer cell types of widely varing differentiation (admixture of glandular, cribiform, and anaplastic morphology within the same cancer). These results clearly demonstrate that prostatic cancer cell heterogeneity can occur early in the clinical course of the disease and there is no requirement for any reduction in serum androgen levels (i.e., no requirement for hormonal therapy) in order to induce this morphological heterogeneity. This last point is also demonstrated by the study of Viola et al. [34] in which immunoperoxidase staining methods were used to examine the cellular distribution of prostate-specific antigen, carcinoembryonic antigen, and p21 Harvey-ras oncogene protein within individual prostatic cancers from patients with metastatic disease who had received no prior hormonal therapy. This study again demonstrates that each of these phenotypic parameters was heterogeneously distributed with multiple foci of both nonreactive and reactive cancer cells present within individual prostatic cancers. Similar cellular heterogeneity within individual prostatic cancers, even before hormonal therapy was initiated, was also demonstrated by Mostofi et al. [35] using immunocytochemical localization of prostatic-specific acid phosplatase as a phenotypic marker.

Based upon these morphological and immunocytochemical studies, it is clear that individual prostatic cancers are heterogeneously composed of clones of phenotypically distinct prostatic cancer cells even before hormonal therapy is begun. This has led a series of investigators [36–39] to suggest that the major reason androgen withdrawal therapy is not curative is not due to an inadequate decrease in the systemic level of androgen following therapy, but is instead due to the fact that prostatic cancers are heterogeneously composed of clones of both androgen-dependent and androgen-independent cancer cells even before hormonal therapy is begun. If this is correct, then treatment of such a heterogeneous prostatic cancer with androgen withdrawal alone would kill only the androgen-dependent clones of cancer cells present, without stopping the continuous clonal growth of the preexisting androgen-independent prostatic cancer cells, no matter how complete this androgen withdrawal therapy might be.

Animal models have clearly demonstrated not only the fact that prostatic cancer can be heterogeneously composed of androgen-dependent and androgen-independent prostatic cancer cells before hormonal therapy is begun [35, 38], but also the fact that an increase in survival above that produced by castration alone cannot be produced, no matter how complete the androgen withdrawal therapy utilized [9]. Using these animal models, it can be shown that an increase in survival, above that produced by castration alone, can only be produced if nonhormonal chemotherapy is given simultaneously in combination with castration, as early as possible, in the course of the disease [40]. In additional studies using Cytoxan as a model chemotherapeutic agent, it has been found that if rats bearing androgen-responsive Dunning R3327-G prostatic cancers are given Cytoxan starting simultaneously at the

time of castration early in the course of the disease, it is possible to increase survival by over 200% in these combinationally treated animals as opposed to tumor-bearing animals simply castrated [41]. Such early, combinational treatment has resulted in 20% of these tumor-bearing animals being cured (i.e., no evidence of disease after 1 year following tumor implantation). In order to cure animals, Cytoxan has to be given simultaneously with, not sequential to, androgen ablation, and it must be started as early as possible and be continued for an extended period [41]. These studies demonstrate that if an effective chemotherapy is available to eliminate the androgen-independent prostatic cancer cells, cures can be obtained if such effective chemotherapy is simultaneously combined with androgen ablation early in the course of the disease [41].

Mechanisms for the development of cellular heterogeneity within individual prostatic cancers

Once a prostatic cancer is heterogeneously composed of clones of both androgen-dependent and androgen-independent cancer cells, androgen withdrawal therapy, no matter how complete, cannot be curative. Therefore, it is critically important to resolve if it is possible to prevent the development of such heterogeneity. To answer this question, some ideas as to the mechanism(s) for such tumor cell heterogeneity must be known.

Multifocal origin of prostatic cancer

One way in which individuals prostatic cancers could be heterogeneous with regard to their androgen responsiveness is that instead of a monoclonal origin for the original prostatic cancers, the tumor could initially arise as a polyclonal mixture of androgen-dependent and androgen-independent cancer cells. This suggestion is strengthened by the observation that when Byar and Mostofi [42] performed careful histological examination of serial step-section on a series of 208 consecutive human prostates removed by radical prostatectomy for early prostatic cancer (i.e., B disease), 85% of the prostates had anatomically distinct multifocal cancer areas. If some of these distinct cancer areas are androgen-dependent and others are androgen-independent, then a heterogeneously responsive tumor would exist even before hormonal therapy is begun. Such a heterogeneous situation could occur rather simply since the normal prostate is heterogeneously composed of both androgen-dependent and androgen-independent prostatic cells even before malignant transformation occurs [43]. The fact that within any individual malignant prostate these multiple cancer foci can have different phenotypic characteristics has been demonstrated by Kirchheim et al. [44]. These authors demonstrate, for example, using histochemical staining techniques, that within the same prostate there can be both cancer foci that are positive and negative for the presence of the enzyme leucine-β-aminopeptidase.

Genetic instability of prostatic cancer cells

Another possibility for the development of heterogeneity in androgen responsiveness within an individual prostatic cancer is that while a prostatic cancer may initially develop monoclonally from a single androgen-dependent malignant cell, as this parental cell continues to proliferate, eventually an occasional progency cell becomes genetically unstable. The concept of genetic instability in cancer cells has been discussed in detail by Nowell [45] and, therefore, the general thesis will not be developed, except to say that genetic instability can eventually lead to changes in the genome of an occasional cancer cell such that a genetically altered clone of cells that is no longer androgen responsive but is now androgen independent can be added to the original homogeneous tumor. When such an addition occurs, the tumor is no longer homogeneous but is instead now heterogeneous. Is there any evidence to support the concept of genetic instability as a mechanism for the development of heterogeneity in androgen responsiveness in prostatic cancer? Using the serial transplantable Dunning R3327 system of rat prostatic cancers, it has been possible consistently to demonstrate that androgen-dependent prostatic cancer cells can randomly give rise to completely androgen-independent cancer cells, even when the original androgen-dependent prostatic cancer cells are grown in an intact (i.e., noncastrated) male host [46]. This progression to the androgen-independent state has been documented to involve genetic instability since definitive changes in the genetic make-up of the prostatic cancer cells have been demonstrated [46, 47]. In addition, Thompons et al. [48] have demonstrated that when an androgen-dependent subline of the Dunning R3327 series is grown in culture, rapid heterogeneity develops such that multiple clones of phenotypically distinct prostatic cancer cells can be isolated. These clonal variations do have in common, however, that they are all androgen independent, even though the original parental cancer cells from which each was derived are initially androgen dependent. Similar loss of androgen dependency of cancer cells during in-vitro culture has also been confirmed by Labrie and Veilleux [4]. Using the Shionogi mouse mammary cancer as a model, this group has confirmed that a wide range of androgen sensitivity develops when clonal variations of the original androgen-dependent Shionogi mammary cancer are grown continuously in culture. Such a heterogeneous distribution of androgen sensitivity develops even if the clonal cells are grown in the continuous presence of physiological levels of androgen. This again confirms that genetic instability of androgen-dependent cancer cells leads to the development of androgen-independent cancer cells and that such development does not require any decrease in the androgenic stimulation to these cells. Such genetic instability thus results in the production of a heterogeneous prostatic cancer, even if the tumor is growing the presence of normal nonablated level of androgen. Once a prostatic cancer is heterogeneously composed of clones of both androgen-dependent and androgen-independent cancer cells, the ability to cure the

patient with androgen ablation alone is lost. This is because even if the clones of androgen-independent prostatic cancer cells are of the androgen-independent sensitive type and are 'hypersensitive' to the low levels of adrenal androgen, as proposed by Labri and Vellieux [4], these clones would not be eliminated, even if total androgen ablation is given, since their growth rate is only sensitive, not absolutely dependent upon, androgenic stimulation.

Conclusions

Androgen-dependent cells within an individual prostatic cancer can be effectively eliminated by any of a series of presently available forms of androgen ablation (e.g., castration, DES, LHRH analogs/antagonists plus/minus anti-androgen). A substantial number of prostatic cancer patients prefer a medical, as opposed to a surgical, form of castration. Since DES produces cardiovascular toxicity, the use of LHRH analogs as a means of medical castration will undoubtedly increase in the future. Due to the flare reaction, an anti-androgen will probably be begun simultaneously with the LHRH analog, and thus the androgen withdrawal therapy combining the two agents will likely become a standard form the therapy for prostatic cancer. This combinational hormonal therapy will probably be as effective as surgical castration; however, it is doubtful whether it will produce a substantial increase in survival compared to simply surgical castration alone. In order to increase survival, what is desperately needed is a modality that can effectively eliminate the clones of androgen-independent cancer cells already present in the prostatic cancer even before therapy is begun. By combining such an effective modality with any of the various types of androgen ablation presently available, it should be possible to affect all of the populations of tumor cells within individual heterogeneous prostatic cancers and thus optimize the possibility for cure. Indeed, this theoretical possibility has been experimentally demonstrated. For example, Cytoxan has sufficient effectiveness against the androgen-independent cancer cells in rat prostatic cancers that if Cytoxan is simultaneously combined with androgen ablation therapy when the tumor is small, cures can be produced. Unfortunately, Cytoxan may not have sufficient effectiveness against the androgen-independent cells within human prostatic cancers to allow cures, even if simultaneously combined with androgen ablation [49]. While combining Cytoxan with androgen ablation has not produced any substantial increase in cures, these previous attempts have usually been begun late in the course of the disease when tumor burden is large and rarely has Cytoxan been begun simultaneously with androgen ablation. In most studies, Cytoxan has been given to patients relapsing to androgen ablation [49]. Servadio et al. [50] has reported, however, on a small group of nonrandomized stage D patients that such combination treatment increases survival above that obtained with androgen ablation alone. Thus, while there is hope that Cytoxan might be helpful when combined with androgen ablation, especially if given earlier in

the disease [51], there are substantial reasons to believe that Cytoxan may not be the optimal agent to control the growth of androgen-independent human prostatic cancer cells. Thus the search for effective agents targeted at the androgen-independent human prostatic cancer cells must continue.

New approaches to control androgen-independent prostatic cancer cells

While the concept of early combinational treatment of prostatic cancer with both hormonal therapy plus chemotherapy is experimentally valid, in order for such an approach to be useful therapeutically in humans, a chemotherapeutic agent that can control the growth of the preexisting androgen-independent prostatic can cancer cells must be developed. There are presently no highly effective chemotherapeutic agents that can control the growth of androgen-independent prostatic cancer cells. There are several possible reasons for this notable lack of success. The most obvious appears to be related to the relatively slow rate of growth of prostatic cancers. Most of the presently available chemotherapeutic agents are targeted at proliferating cancer cells, therefore, it is not surprising that there is a good correlation in a large variety of cancers between the effectiveness of these agents and the respective cancer's rate of cell proliferation [52]. These previous studies have demonstrated that in cancers with high cell proliferation rates, chemotherapy can achieve high initial fractional cell kills per course of therapy, producing complete clinical responses. In contrast, in cancers with a low cell proliferation rate, it has been found that the fractional cell kills are small, producing partial responses and shallow complete responses at best. The strong correlation between a high cell proliferation rate and chemotherapeutic sensitivity in human cancer is demonstrated from the studies of Tubiana and Malaise [53]. These data affirm that slow-growing cancers have very low rates of cell proliferation and respond with small fractional cell kills per course of therapy.

These data also suggest that in order for chemotherapy to be effective, not only the rate of cell proliferation, but also the rate of cell death, must be high. The importance of this statement is emphasized by the following two examples using the data of Tubiana and Malaise [53]. In an average embryonal cancer, approximately 44% of the cell are proliferating per day and 41% of the cells are dying per day. If this embryonal cancer is treated with a chemotherapeutic agent that produces a decrease in the cell proliferation rate of as little as 10% (i.e., changes it from 44% to 40% per day) with no effect on the daily cell death rate, then the cancer will actually involute since the rate of cell death (i.e., 41% per day) is now greater than the rate of cell proliferation (i.e., 40% per day). In contrast, in a typical adenocarcinoma, approximately 2.9% of the cells are proliferating per day and 2.0% are dying per day. If this adenocarcinoma is treated with a chemotherapeutic agent that reduces the daily cell proliferation rate by 10% (i.e.,

changes it from 2.9% to 2.6% per day) with no effect on the daily cell death rate, then the cancer will still continue to grow, since the rate of cell proliferation (i.e., 2.6% per day) is still greater than the rate of cell death (i.e., 2.0% per day). In fact, it can be calculated from cell kinetic equations [54] that this response will only change the tumor doubling time of the adenocarcinoma from 83 to 116 days, a response having little effect upon host survival. These examples demonstrate that if the daily cell death rate in a cancer is high enough, then antiproliferative chemotherapy that induces even a small (e.g., 10%) reduction in the daily cell proliferation rate can produce tumor regression, resulting in a high rate of complete durable response (e.g., a fast-growing cancer). In contrast, if the daily cell death rate is too low (i.e., in slow-growing cancers), then antiproliferative chemotherapy must induce a much larger reduction in the daily cell proliferation rate (i.e., a large fractional cell kill) to produce a similar response. Unfortunately, the fractional cell kills achievable at maximum tolerated therapeutic intensity in slow-growing cancers are not high enough to produce high complete response rates or durable complete responses [52]. These examples demonstrate that a high death rate is critically important in allowing even small decreases in the cell proliferation rates, induced by chemotherapy, to be clinically useful.

While the exact magnitude of the daily cell proliferation rate has been determined for only a small number of human prostatic cancer patients [55, 56], the published results demonstrate that prostatic cancers are typical of most other solid adenocarcinomas in their low rate of cell production. The daily rate of cell death has not been precisely determined for any human prostatic cancers, but from preliminary analysis, it would appear to be in the same low range as for other slow-growing solid cancers. This would suggest that the successful treatment of slow-growing prostatic cancers will require simultaneous androgen ablation for the removal of the androgen-responsive clones of tumor cells coupled with chemotherapy targeted at the androgen-independent clones of cells. The chemotherapy itself may have to include two different types of agents: one agent having antiproliferating activity affecting the small number of dividing androgen-independent cells and the other agent targeted at increasing the low rate of cell death among the majority of nonproliferating androgen-independent prostatic cancer cells present. Since there appears to be a large variety of adequate antiproliferative chemotherapeutic agents presently available, it would appear most appropriate for the future to attempt to develop new agents of the latter type specificially targeted at increasing the rate of cell death of nondividing cancer cells. Along these lines, recent studies have demonstrated that the involution of the normal prostate following androgen withdrawal is due to activation of a series (i.e., cascade) of discreet biochemical steps induced by androgen withdrawal leading to the 'programmed death' of the androgen-dependent cell within the prostate [57]. This programmed cell death is an active process and involves a calcium-activated endonuclease activity [57]. Studies are presently being performed to determine if androgen-independent prostatic cancer

cells can be made to undergo this same programmed cell death by nonhormonal agents that activate the cascade distal to the point normally blocked by androgens.

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11. Mechanisms of action of intravesical bacillus Calmette-Guerin for bladder cancer*

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Introduction

The use of bacteria as an immunomodulatory agent in cancer therapy was first documented in the early 1900s when Coley demonstrated tumor regression of advanced tumors with injection of microbial extracts [1]. During the 1960s, bacillus Calmette–Guerin (BCG) was noted to impart a prolonged remission in several small studies involving leukemia patients [2]. Larger cooperative studies prompted by these early successes, however, proved to be less encouraging. Throughout the early 1970s multiple studies evaluating the therapeutic effect of BCG on several tumor systems were carried out. The equivocal and somewhat disappointing results coincident with the development of new, more effective chemotherapeutic regimens resulted in a loss of initial enthusiasm.

The lack of efficacy observed in most clinical trials was attributed to a lack of direct toxicity for tumor cells by BCG and also to limitations of the host immune response. The criteria considered necessary for successful BCG therapy were developed by Zbar and Rapp [3] based on their preclinical studies and are summarized as follows: 1) close contact between the tumor cells and BCG; 2) immunocompetence of the host, i.e., the ability of the host to mount a delayed cutaneous hypersensitivity response to mycobacterial antigens is required; 3) effective treatment is restricted by tumor size such that therapy is ineffective against large tumors; and 4) an adequate number of viable bacteria are necessary. Most of the clinical studies on advanced non-bladder tumors were not successful, presumably because they did not meet these criteria.

In 1975, Bloomberg and associates demonstrated that an inflammatory reaction comprised of histiocytes and leukcocytes was induced in the bladder of BCG-sensitized dogs following BCG instillation [4]. These studies demonstrated the potential for expression of delayed hypersensitivity in the bladder and prompted Morales to evaluate the potential of BCG immunotherapy for

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the treatment of superficial bladder cancer [5]. It is this tumor system in which the beneficial effects of BCG have been most consistently documented, possibly because superficial bladder cancer most often adheres to the conditions proposed by Zbar and Rapp for maximum efficacy.

BCG therapy for superficial bladder cancer

Papillary tumors

Results from the first clinical trial of intravesical BCG in patients with recurrent superficial bladder tumors were published in 1976 by Morales. Treatment consisted of intradermal BCG and 120 mg of BCG [10^7 colony forming units (CFU)/mg] in 50 ml of saline instilled intravesically once a week for 6 weeks. Patients were followed every 3 months with cystoscopy and bladder biopsies. BCG therapy reduced tumor recurrence to one recurrence per 41 patient months compared with 22 tumor recurrences in 77 patient months among the patients prior to BCG therapy [5].

Two early prospective randomized trials confirmed the initial promising results. Commancho and associates [6] randomized 86 patients to receive either conventional therapy consisting of transurethral resection alone or transurethral resection followed by intravesical instillation of BCG as described by Morales. Results were subsequently reported in terms of tumor recurrence per patient month. Pretreatment recurrence rates for the BCG and control groups were 3.60 and 2.97 per patient month, respectively. Following treatment there was a significant reduction ($p < .011$) in the tumor recurrence rate for the BCG therapy group (0.75 tumors per patient month), while the control group remain unchanged (2.37 tumors per patient month).

The second prospective randomized trial conducted by Lamm and associates [7] was comprised of 51 patients randomized to control (27 patients) and BCG treatment groups (24 patients). Controls were treated with transurethral resection alone, while the BCG group received adjuvant intravesical BCG, as described by Morales. Follow-up cystoscopic examinations showed a recurrence of 46% (11 of 24 patients) in the control group and a recurrence of 22% (5 of 23 patients) in the BCG treatment group. The mean time to recurrence was also extended by BCG therapy, with controls being 16 months while the BCG group was 29 months.

In 1982, Brosman conducted a prospective randomized clinical trial with a total of 49 patients, comparing adjuvant intravesical thiotepa with adjuvant intravesical BCG for recurrent superficial bladder cancer. After 2 years of follow-up, 19 patients (40% of the thiotepa therapy arm) developed recurrent tumors, while no recurrences were noted in either the 27 randomized BCG patients or in the 12 nonrandomized patients who also received BCG therapy [8].

More recently, Mori, Lamm, and Crawford [9] reported data demonstrating

that BCG immunotherapy was superior to adjuvant Adriamycin chemotherapy in the treatment of recurrent transitional cell carcinoma and carcinoma in situ of the bladder. Recurrence rates of 19% (16 of 88 patients) were observed in the BCG treatment group compared to 54% (45 of 83 patients) in the Adriamycin treatment group.

These prospective randomized trials have verified the initial results of Morales and established intravesical BCG as an effective treatment for bladder cancer. They have also suggested that BCG is superior to currently available adjuvant intravesical chemotherapy regimens. However, despite the efficacy of BCG, which has been supported by randomized trials, general acceptance has been a slow process, requiring the accumulation of an extensive irrefutable data base.

Carcinoma in situ

Equally remarkable are the results of BCG treatment for carcinoma in situ (CIS). Several studies have reported favorable long-term results with intravesical BCG for the treatment of CIS, making it an appropriate alternative to radical surgery as a first-line treatment for CIS. Morales [10] first published favorable results in which five of seven patients with CIS of the bladder were rendered tumor free, with a mean follow-up of 22.6 months. A long-term follow-up by Herr et al. [11] compared 47 patients treated with BCG both separately (24 patients) and as part of a randomized control study (23 patients) with a group of 26 patients treated by transurethral resection and fulgeration alone. Of the 47 patients treated with BCG, 32 (68%) were free of disease, with a follow-up of 51 and 45 months for the two groups. Of the 23 control patients in the randomized study, there were no tumor-free responses. In addition, cystectomy for disease progression was required in 17 of 26 control patients (65%) compared with only 4 (17%) in the BCG treatment group.

Brosman has also documented long-term, tumor-free responses (mean 5.25 years of follow-up) in 27 of 33 patients [12]. Finally, Morales and Nickel [13] demonstrated a complete response in 20 of 26 (77%) patients with BCG-treated CIS, with a mean follow-up of 4 years.

Optimal treatment regimen

Although several different treatment regimens have provided good therapeutic results, the most efficacious regimen is not known. The most important topics in need of clarification today are duration or intensity of therapy and whether there is a need for maintenance therapy after the initial induction phase.

Our studies Washington University School of Medicine have evaluated 104 patients with superficial bladder tumors for response to six weekly intravesical instillations of BCG. Treatment failures consisted of those patients with cy-

tology or biopsies positive for tumor. Patients who failed the initial treatment course of weekly intravesical instillations for 6 weeks were given an additional 6 weeks of therapy. The response rate for the total population treated with one 6-week course was 37.5% (39 of 104). However, the response rate for all patients receiving a second course of BCG was 59.6% (34 of 57). The total response rate for patients receiving either one or two 6-week courses was 70% (73 of 104), with a tumor-free follow-up approaching 2 years. These results suggest that weekly intravesical instillations for 6 consecutive weeks of BCG do not provide optimal therapeutic results and are supported by reports by Brosman [12] and Brendler and Alexander [14], who observed an increase in tumor-free response by increasing the number of weekly instillations. In contrast, others [15, 16] report rates similar to ours (70%) with only 6 weeks of instillation.

The use of maintenance BCG following an induction course of BCG also remains controversial. Several investigators believe that maintenance therapy is beneficial, citing a theoretical advantage of continued antigenic stimulation within the bladder as a means of enhancing antitumor activity. Several studies [12, 16] have advocated the use of maintenance BCG therapy. Unfortunately patient number in both of these studies is small, 33 patients and 30 patients, respectively, and more importantly, the comparison is historical and not prospectively randomized.

We have reported a prospectively randomized trial comparing the efficacy of BCG therapy with and without quarterly maintenance instillations for 42 patients. Overall no differences were noted in the bladder tumor recurrence rates between the maintenance and single course groups [17]. These findings were similar to those reported in a recent prospective randomized trial of maintenance versus nonmaintenance intravesical BCG published by Badalamet and associates [18] that considered 93 patients.

An important consideration was the increase in adverse side effects that occurred in those patients receiving maintenance doses in the Washington University protocol. The two most serious cases being that of epididymo-orchitis, one of which required an orchiectomy. The most common side effects were those of dysuria with irritative voiding symptoms. Fever, chills, and flulike symptoms recurred with each maintenance dose in almost half of the patients who originally experienced them. It would then appear that, to date, published data in the form of two separate prospective randomized studies show that nonmaintenance protocols are the regimen of choice.

In summary, intravesical BCG therapy has proven to be efficacious as an adjuvant treatment with transurethral resection and fulgeration for superficial bladder cancer including carcinoma in situ. This has been established by several prospective randomized studies documenting both short-term, as well as long-term, tumor-free responses. In addition, BCG appears to be superior to other forms of intravesical therapy, i.e., Adriamycin and thiotepa. Further prospective studies are needed to more clearly define optimal treatment duration as well as the need for maintenance doses of BCG.

Mechanisms of BCG action

The treatment of recurrent superficial transitional cell carcinoma (TCCA) of the bladder by intravesical instillation of BCG appears to provide an effective means of inhibiting tumor recurrence. The mechanisms by which intravesical BCG inhibit this growth are not known. Intravesical BCG for superficial bladder cancer has been termed by some as a form of immunotherapy [17], but others have suggested that nonimmune mechanisms may be involved [19].

Understanding the mechanisms by which BCG works could be far reaching. This knowledge could provide a basis for developing immunotherapy protocols for nonbladder cancers, for better selection of patients for bladder cancer therapy, and for monitoring the progress of bladder cancer therapy. Furthermore, a clear understanding of these mechanisms, whether immunological or nonimmunological, could lead to therapy without the need for treating with viable, potentially infective bacteria.

This review will discuss available evidence concerning potential mechanisms of action and define areas in which further investigations are needed. Cancer immunotherapy may be defined as an immunological response that leads to the destruction of the tumor. The response may be directed against antigens present on a tumor (specific immunotherapy) or the response may be initiated by recognition of BCG antigens that result in a cascade of nonspecific immunological events leading to tumor destruction (nonspecific immunotherapy). Nonimmunologic mechanisms include direct toxicity of BCG organisms to bladder tumor cells and inflammatory events in the absence of antigenic recognition.

Nonimmunologic mechanisms

Nonimmunologic mechanisms include either a direct toxic effect of BCG organisms for tumor cells or acute inflammation producing a condition that may impede blood flow and result in ischemic necrosis. There are no published reports that show direct toxicity of BCG to bladder tumor cells. In our own studies we have observed no toxic effects of BCG for the mouse bladder tumor, MBT-2, or the human bladder cancer cell line, T-24, during in-vitro coculture [T.L. Ratliff, unpublished]. Moreover, intravesical BCG therapy for bladder tumors implanted in immunodeficient mice (athymic nude mice) did not inhibit tumor growth. These animals received the same exposure to BCG as immunologically intact mice. If direct toxicity were a primary mechanism, one would expect to observe antitumor activity in the immune-deficient mice.

Acute inflammation resulting in cystitis is a second nonimmunologic mechanism. Intravesical BCG therapy induces cystitis but it is of a chronic nature. Cystitis is also induced by chemotherapeutic agents used in intravesical therapy such as Adriamycin, which has been shown to be inferior to BCG.

To determine whether inflammation alone mediated antitumor activity,

Lamm and associates [20] treated MBT-2 mouse bladder tumors intralesionally with BCG cell-wall skeletons. The cell-wall skeletons had no effect on MBT-2 growth, suggesting that chronic inflammation alone is not sufficient for antitumor activity.

Experiments using the L-10 hepatoma tumor model provide direct evidence that acute and chronic inflammation alone do not inhibit tumor growth. Hanna, Zbar, and Rapp [21] showed that neither vaccinia virus, oxazolone, nor turpentine inhibited L-10 growth. Acute inflammation for each compound was histologically documented and characterized, leaving no doubt that acute inflammation alone was not the mechanism of action of BCG in the L-10 model. Moreover, nonviable BCG were not effective in this model, suggesting that chronic inflammation alone was not sufficient for mediating antitumor activity.

Other studies offer indirect evidence that nonimmunologic inflammation is not associated with BCG-induced antitumor activity. In the L-10 model, BCG was not effective in guinea pigs with depressed T-lymphocyte responses [22]. It is well documented that acute as well as chronic inflammation with granuloma formation occurs in the absence of immunologic recognition, but such a response is not sufficient in the L-10 model for mediation of antitumor activity. At Washington University School of Medicine, we have observed similar results using the MBT-2 mouse bladder tumor in athymic nude mice. No antitumor activity was observed in the absence of a T-lymphocyte response; however, adoptive transfer of BCG-sensitized spleen cells restored BCG-induced antitumor activity [23].

In conclusion, considerable evidence exists that suggests nonimmunologic mechanisms are not associated with the antitumor activity of BCG. One may conclude, based on the available evidence, that immunologic mechanisms appear more likely to be associated with effective intravesical BCG therapy.

Immunologic mechanisms

The participation of immunologic mechanisms in intravesical BCG therapy is suggested by indirect data from several research groups; however, definitve evidence is lacking for both clinical and animal studies.

Immunological mechanisms are divided into two categories, specific and nonspecific responses, which were defined above. The specific response is further divided into antibody (humoral) and cellular mechanisms. The relative roles of these mechanisms will be examined below.

Specific immunological mechanisms. Involvement of specific immunologic responses, either humoral or cell-mediated, in the elimination of bladder tumors dictates the presence of recognizable antigenic determinants on bladder tumor cells. Evidence for the presence of tumor-associated antigens on human bladder tumors is indirect but suggestive. Several investigators have reported the presence of serum antibodies from tumor-bearing patients

that specifically recognized bladder tumors [24, 25]. Furthermore, bladder-tumor antigen preparations have been shown to induce lymphokine production by lymphocytes from bladder-tumor patients. Lymphokine production was specific in that tumors of other histologic origin did not induce production, and production was not induced in lymphocyte preparations from nonbladder cancer patients [26]. More recent studies showed that mouse monoclonal antibodies developed from bladder-tumor immunization procedures offer some specificity [27]. Taken together these data suggest that tumor-associated antigens are expressed on human bladder tumors, and thus specific immunologic responses must be considered as potential mechanisms of action of intravesical BCG therapy.

The animal model most used for studies on bladder cancer is the mouse bladder tumor, MBT-2, developed by Soloway and associates [28]. The expression of tumor-associated antigens on this tumor is similar to that described in clinical specimens. Transplantation studies have shown that the tumor is weakly immunogenic [29]. Sensitization with MBT-2 cells results in partial protection, which can be detected only by reducing the initial tumor innoculum to a level that produces tumors in approximately 50% of mice. Even at this level, the protection is not complete.

Hellstrom and associates [30] have reported the development of monoclonal antibodies to tumor-associated antigens on MBT-2 tumors. These antibodies express specificity similar to those developed from clinical specimens.

These data show similarities between the MBT-2 tumor model and clinical findings and thus establish the MBT-2 tumor as a useful model for studying the immunological mechanisms of action of intravesical BCG.

Humoral mechanisms. Data examining the potential role of antibodies in intravesical BCG therapy are practically nonexistent. It is well known that BCG has an adjuvant effect on antibody production to antigens of diverse origin, including syngeneic tumors [31]. Whether antibodies to bladder tumors are produced after BCG therapy remains to be established.

Winters and Lamm [32] studied patients receiving BCG for serum antibodies recognizing BCG antigens. These antibodies were shown to increase during combined intravesical and intradermal BCG therapy. Winters and Lamm suggested that antibodies recognizing BCG antigens may crossreact with bladder TCCa antigens. There are reports suggesting that some tumor cells do possess antigenic determinants crossreactive with BCG antigens [33]; however, Winters and Lamm provided no evidence that crossreactive antibodies were present in BCG therapy patients. This is the only published data concerning humoral mechanisms that represents a hypothetical possibility with little supporting evidence. A recent report by Haspel and associates [34] documents the production of antibodies reactive with colon carcinoma cells after administration of a BCG-tumor-cell vaccine to tumor-bearing patients. This report provides further evidence supporting the potential for antibody production in bladder cancer patients.

Cell-mediated mechanisms. There are no clinical data implicating the presence of a specific T-lymphocyte response to tumor-associated antigens in bladder-cancer patients treated with BCG. Only limited data in bladder tumor models are available.

Reichert and Lamm [35] suggested that long-term immunity was induced in mice bearing the mouse bladder tumor, MBT-2, treated with intralesional BCG. Mice surviving the initial treatment course were rechallenged with MBT-2 tumors and only 56% developed tumors. Additional intralesional BCG did not enhance the antitumor effect. These experiments suggested the presence of a specific response to MBT-2 antigens; however, the experiments lack appropriate tumor specificity controls and do not directly demonstrate the presence of immune cells with specificity for MBT-2 cells. Since the response was not defined, these data could support the presence of either a cellular or humoral response. Additional studies must be performed to confirm this preliminary observation and to identify the immunologic mechanisms.

Other tumor models for which BCG therapy has been tested have shown variability in the development of specific cellular responses to tumors [36]. Studies on the role of specific cellular responses in the L-10 guinea-pig hepatoma model show that specific cellular responses are present [37]. Guinea pigs that eliminated tumors after intralesional BCG treatment expressed long-term resistance to L-10 tumors. Mice receiving only L-10 tumor cells did not inhibit the growth of a second tumor challenge. Furthermore, the growth inhibitory activity of BCG-treated L-10 immune mice was specific for the L-10 tumor, since the growth of antigenically distinct tumors were not inhibited by the L-10 sensitized animals.

Studies on other tumor models show that antitumor immunity, i.e., recognition of tumor-associated antigens by syngeneic hosts, is not required for effective BCG-mediated antitumor activity, although T cell responses to BCG were required [36]. Taken together, the data show that either or both tumor antigen recognition and recognition of BCG antigens may be important in BCG-mediated antitumor mechanisms, depending on the tumor model being studied. Thus, it is a distinct possibility that specific antitumor immunity may be associated with destruction of bladder tumors. Additional work is needed to more clearly define the role of tumor-specific immunity in the bladder tumor.

Nonspecific immunological mechanisms. Nonspecific immunologic mechanisms involve the antigenic recognition of BCG antigens, which result in the initiation of a cascade of events that ultimately kill bladder tumor cells. The mechanisms can include either lymphokine or nonspecific, cell-mediated, tumor-cell killing.

Clinical studies. Clinical studies suggest a link between a patient's response to BCG antigens and response to therapy. Lamm and associates [7] have shown that a delayed cutaneous hypersensitivity (DTH) response to purified protein

derivative (PPD) correlated well with the therapeutic response to BCG. Only 1 of 17 (6%) patients who converted from PPD negative to PPD positive with therapy developed recurrent tumors, while 38% of those either remaining negative or who were PPD positive upon entering therapy developed tumor recurrence.

Kelley and associates [38] also reported a correlation between PPD responsiveness and therapeutic efficacy. A significant correlation ($p < .0006$) was observed between DTH to PPD and treatment results. Among patients who were initially PPD positive (5 patients) and those who converted their skin tests to positive (25 patients), tumor persisted or recurred in only 6 of 30 (20%). In contrast, tumors persisted or recurred in 21 of 32 (66%) who did not convert their PPD skin test.

Kelley and associates [38] further showed that granulomatous inflammation in bladder biopsy specimens obtained 6 weeks after completion of therapy also significantly correlated ($p < .003$) with a favorable response to therapy.

Taken together these results suggest that a DTH-induced inflammatory response is closely associated with response to intravesical BCG therapy: however, the data are only suggestive, and more direct evidence is needed to establish a firm link.

Studies to define an effector response. As stated above, the mechanism by which BCG treatment for bladder cancer inhibits tumor growth is not known. However, a considerable body of evidence, specifically those clinical studies showing an association between development of DTH by measuring PPD conversion and a favorable prognosis, implicates an immunological mechanism for this antitumor activity. This section will discuss some of the work that has attempted to characterize the effector response of the BCG-induced immunologic mechanism.

Pang annd Morales [39] showed that an intraperitoneal injection of 10 mg (10^8 CFU) BCG induced regression of subcutaneously implanted MBT-2 tumors in 50% to 90% of treated mice. Analysis of the peritoneal exudate cells revealed that BCG-induced non specific cytotoxic cells expressed a natural killer cell phenotype. This data led Pang and Morales to suggest that natural killer cells were associated with the antitumor activity of BCG. No attempts were made, however, to identify the lymphoid cells infiltrating the regressing tumor, nor were specific studies reported to determine whether cured mice could reject subsequent MBT-2 challenge.

Shapiro and associates [40] reported a significant correlation between augmentation of natural killer cell activity of splenocytes and efficacy of intravesical BCG therapy. In this model, MBT-2 tumor cells were implanted intravesically. The level of both natural killer cell activity and antitumor activity were dependent upon the dose of BCG. Moreover, in a second series of experiments, depressed natural killer cell activity was associated with a lack of antitumor activity. These results supported the hypothesis presented by Pang and Morales linking natural killer cell activity with BCG-mediated

antitumor activity, however, direct evidence linking natural killer cells to BCG-mediated antitumor activity remained lacking.

Ratliff and associates [41] performed further experiments in attempts to provide more direct evidence linking natural killer cell activity to the antitumor affects of BCG. Antiasialo GM serum, which has been demonstrated to abrogate natural killer cell activity without significantly altering T lymphocyte, B lymphocyte, or macrophage responses, was administered to mice prior to initiation of BCG therapy and at 5-day intervals throughout therapy. Natural killer cell activity was demonstrated to be depressed in the spleen and iliac lymph nodes throughout therapy. The depression of NK activity had no effect on BCG-mediated antitumor activity. These data provide the most direct evidence to date that natural killer cells are not the primary mechanism of BCG-mediated antitumor activity; however, antiasialo serum is not specific for natural killer cells. More specific methods of abrogating natural killer cell activity need to be developed to confirm the observation. In addition, locally infiltrating cells conceivably could escape the effects of antiasialo GM and would remain undetected in an analysis of splenocyte and lymph-node cell cytotoxicity. Although more definitive data are needed, the data suggest that BCG-mediated natural killer cell modulation is independent of the antitumor mechanisms.

Other animal tumor models have been studied that suggest nonspecific immunologic mechanisms are associated with BCG-mediated antitumor activity. Bartlett, Zbar, and Rapp [36] showed that both immunogenic and nonimmunogenic tumors were rejected when injected together with BCG, while a contralateral injection of BCG had no effect on tumor growth. Bartlett demonstrated that a DTH response to BCG without concomitant development of tumor-specific immunity mediated inhibition of tumor growth. These data suggest that bystander killing, i.e., the nonspecific killing of tumor cells by mononuclear cells activated by a specific response to BCG, is important in tumor rejection. Studies in other systems, however, have shown that the development of the DTH response alone is not sufficient for inhibition of tumor growth. Injection of PPD or dinitrophenyl poly-L-lysine in the tumors of immunized animals was not sufficient to induce tumor regression, even though a DTH response to these antigens developed. Injection of soluble factors induced a DTH inflammatory response indistinguishable from the BCG-induced response during the first 4 days. After this time interval, the BCG response became chronic with the development of granulomas, while the response to the other stimuli receded. These results suggest that granuloma formation, with its accompanying chronic macrophage response, is required for effective inhibition of tumor growth.

Histological and ultrastructural studies strongly implicate cells of the macrophage-moncyte lineage in antitumor activity of BCG. These results show that macrophages are the primary infiltrating cell and suggest that the cytopathic effect of activated macrophages is mediated both at the primary tumor site and in regional lymph nodes by nonphagocytic mechanisms

involving direct cell-surface contact. In this regard, macrophages isolated from animals injected with BCG and tumor cells have been shown to be cytotoxic in vitro. However, direct evidence implicating macrophages as an effector cell is lacking.

Ratliff et al. [23] demonstrated that the antitumor activity of intravesical BCG therapy may require a thymus-dependent immune response. Intravesical BCG was demonstrated to have no antitumor activity when administered to athymic nude mice bearing MBT-2 tumors. However, adoptive transfer of BCG-sensitized splenocytes (one spleen equivalent per mouse, IV), immediately prior to the first BCG treatment, transferred delayed-type hypersensitivity. Adoptive transfer also restored the antitumor activity of intravesical BCG.

These results do not identify the specific aspect of the thymus-dependent response associated with antitumor activity. Several T-lymphocyte responses could mediate an antitumor response, including cytolytic T lymphocytes, production of cytotoxic lymphokines, helper T-lymphocyte activity associated with antitumor antibody production, and lymphokine-mediated activation of nonspecific, cell-mediated cytolytic mechanisms. Additional studies will be required to identify these participating responses.

Little data is available concerning the role of lymphokines in the inhibition of bladder tumor growth by BCG. Haaff and associates [42] found that interleukin-2, a T-lymphocyte-derived growth factor, was present in urine specimens of BCG-treated patients only after BCG instillation. Detectable interleukin-2 levels were present for prolonged periods (at least 7 hours), showing that the potential exists for prolonged exposure of bladder tumors to cytotoxic and cytostatic lymphokines.

In-vitro experiments have shown that bladder tumor cells are susceptible to the antiproliferative properties of interferon gamma (a T-cell-derived lymphokine). Whether lymphokines such as interferon gamma, lymphotoxin, or tumor necrosis factor are actively involved in the antitumor activity of BCG remains to be established. Similar hypothetical potential mechanisms can be presented for lymphokine-activated killer cells and other nonspecific mechanisms.

Factors affecting the initiation of antibladder tumor activity

The studies discussed above outline our knowledge concerning potential effector mechanisms in BCG therapy. It is clear from these studies that BCG is retained and internalized after intravesical instillation alone, since patients express systemic immunological responses, and granulomatous inflammation is observed in the bladder. Thus, the events surrounding the retention and internalization of BCG are important to our understanding of the initiation of the antitumor response. Our studies on the initiation events suggest that in the mouse tumor model, BCG attachment to fibronectin (FN) exposed on

the bladder wall is a requisite step for the development of an immunolgic response and for the expression of both delayed-type hypersensitivity and antitumor activity within the bladder.

Fibronectin is a dimeric glycoprotein found in blood, body fluids, and connective tissue matrices. It plays an important role in the function of cell adhesion, cell motility, and the interaction between cells and connective tissues of the basement membranes. The molecule is composed of two disulfide-bonded 210–250 kd subunit polypeptides and possesses several specific binding sites, including sites specific for a number of macromolecules, i.e., collagen, fibrin, heparin sulfate, dextran sulfate, and DNA [43].

Spectrophotometric and ultracentrifugation experiments have shown that cellular and plasma fibronectin are elongated molecules composed of three distinct repeating subunits, separated by flexible extrudable regions of polypeptide chains. Each arm of the functional dimer can be divided into functional domains, often referred to by one of the substances that bind to that region. For example, domain 1 and domain 8 are referred to as *fibrin-binding domains*, domain 2 is the *collagen/gelatin-binding domain*, domain 6 is the *cell-adhesion region*, and domain 9 is the *carboxy terminus* [43].

Several investigators have revealed specific fibronectin binding sites for bacteria. Kuusela and associates [44] for example, have demonstrated the attachment of *Staphylococcus aureus* (Cowan 1) and two strains of group A and G steptococci on glass coverslips coated with fibronectin. The use of fibronectin fragments demonstrated enhanced binding to the 30 kd amino terminal and the 120–140 kd carboxy terminal regions of fibronectin, suggesting that both parts of the molecule are involved in the attachment mediated by intact fibronectin.

Other studies [45] have isolated a fibronectin-binding protein for *Staphylococcus aureus*. The 210 kd fibronectin-binding protein was isolated from a bacterial lysate by affinity chromatography followed by gel chromatography. Smaller peptides with fibronectin-binding properties were also obtained, which probably represented degradation products of the larger receptor. This suggests that the larger receptor protein probably contains several binding sites for the fibronectin molecule. The binding of streptococci, specifically lipotichoic acid (LTA) from the gram-positive cell wall, to fibronectin has also been demonstrated [46]. In this investigation, a Scatchard plot analysis revealed at least one population of high-affinity binding sites, with a binding affinity two orders of magnitude greater than the binding affinity of serum albumin. This interaction of fibronectin with streptococci occurs at a domain distinct from the domain that binds *S. aureus* and is located near the amino terminus of the molecule.

The significance of these observations remains to be determined, though it may be assumed that these in-vitro studies may be extrapolated to in-vivo situations. Insoluble fibronectin is found in most human cell types and at matrix surfaces, and possibly may mediate attachment of invading organisms, helping pathogens to establish cells in tissues and initiate infection.

Fibronectin binding of *Treponema pallidum* may be involved in the initial adherence of that pathogen to host tissues, as well as being an important component of the immune complexes formed by patients with syphilis [47]. Finally, other investigators have shown that fibronectin appears to promote the adherence of fungi [48], parasites [49], and viruses [50] to host tissues.

Fibronectin and its role in initiation of BCG-mediated antitumor activity

Our initial studies involved histological analysis of BCG attachment to mouse bladders [51]. BCG was instilled into normal bladders and bladders damaged by electrocautery. Acid-fast stains demonstrated attachment of BCG in cauterized bladders only. Quantitative experiments verified the histologic observations. Minimal BCG attachment (mean $<10^2$ colony forming units) was noted in normal bladders, in contrast with the mean of 1.42×10^4 colony forming units/bladder in bladders damaged by electrocautery.

To investigate the proteins to which BCG attached, the binding of BCG to various inflammatory and extracellular matrix proteins comprising the fibrin clot was tested. BCG were found to bind in vitro to surfaces coated in vivo with extracellular matrix proteins but not to control albumin-coated coverslips. BCG also bound to coverslips coated with purified plasma fibronectin, but not other purified extracellular matrix proteins, including laminin, fibrinogen, and Type IV collagen. BCG attachment to surfaces coated with either a mixture of extracellular matrix proteins or purified fibronectin was inhibited by antibodies specific for fibronectin. In addition, BCG attachment to cauterized bladders in vivo was inhibited by antifibronectin antibodies. These results demonstrated that fibronectin mediated the attachment of BCG to coated surfaces and, more importantly, that it apparently acted as the primary component mediating attachment within the bladder.

Further studies confirmed the initial hypothesis. Evidence was obtained suggesting that fibronectin-mediated attachment is the necessary first step for the expression of both an immune response and antitumor activity. In a recent study, delayed-type hypersensitivity (DTH) to mycobacterial antigens was quantified by measuring accumulation of ^{125}I-UDR in the bladder after instillation of BCG, as described by Thomas and Schrader [52]. Significant delayed-type hypersensitivity was measured (mononuclear cell accumulation verified histologically) in BCG-sensitized mice treated intravesically with BCG. Inhibition of BCG attachment to the bladder wall inhibited the expression of DTH response in sensitized mice.

The necessity of BCG binding to fibronectin for the expression of antitumor activity was also tested. C3H/HEJ mice were anesthetized and cauterized. MBT-2 tumors were implanted in cauterized mice and BCG treatment was initiated 24 hours later and weekly thereafter. In a second group of mice, BCG attachment was inhibited by pretreating BCG with fibronectin (demonstrated to block BCG attachment). It was determined that untreated BCG

significantly reduced MBT-2 tumor outgrowth, whereas fibronectin-pretreated BCG did not significantly alter MBT-2 outgrowth.

Binding between BCG and soluble fibronectin has also been demonstrated [J. Aslanzadeh, unpublished]. This binding was found to be similar to the binding interaction described for staphylococci and streptococci, in that binding was most likely receptor mediated, rapidly saturable (reaching equilibrium in 3 minutes), and essentially irreversible. Scatchard analysis of the fibronectin/BCG interaction demonstrated approximately 8000 to 15,000 receptors per bacterium with an association constant of 9.0×10^{-9}. The Scatchard plot provided a straight line, suggesting that one receptor class was present.

In contrast to previous observations with *S. aureus*, which showed enhancement of soluble fibronectin binding in the presence of sodium chloride, soluble fibronectin binding to BCG was inhibited by the presence of as little as 0.15 M NaCL. NaC1 in concentration up to 0.5 M did not inhibit BCG attachment to fibronectin-coated surfaces. In addition, the pH range for fibronectin binding to BCG also differed from that of *S. aureus*, in that BCG binding to fibronectin occurred at an acidic pH, with a lower level of binding occurring at neutral or basic pH. Since we observed that binding of soluble fibronectin to BCG prior to intravesical instillation inhibits attachment of BCG to the bladder wall, the potential of blocking BCG attachment to the bladder wall by soluble fibronectin is present. These findings suggest that a diluent for BCG should have a neutral or basic pH and should be supplemented with at least 0.15 m NaC1. Such a diluent would decrease the potential inhibition of BCG attachment to the bladder wall by minimizing the binding of soluble fibronectin.

The attachment of BCG to the bladder wall via fibronectin may be important to the antitumor activity of BCG for several reasons. It may function in a passive manner as an attachment matrix mediating retention of BCG and allowing induction of an immune response to the organism. The expression of this anti-BCG immune response within the bladder may then eliminate the tumors. Fibronectin may also play a more active role in the induction of the immune response and expression of antitumor activity. Since fibronectin may be opsonic, it may direct BCG to macrophages for processing and presentation to the immune system. Furthermore, by entering the macrophage complexed to BCG, fibronectin could become the target of the immune response as an altered self-antigen.

In summary, a requisite first step in the initiation of an immune response is introduction of the antigen to the immune system. Results of recent experiments at Washington University suggest that fibronectin plays an important role in this step. Fibronectin, which is preferentially distributed throughout the basement membrane of the bladder urothelium, appears to mediate attachment of BCG to areas of disrupted mucosa. This attachment has been demonstrated in both in-vivo and in-vitro conditions. It appears to be receptor mediated, is relatively irreversible, and is blocked by pretreatment with antifibronectin antibodies. Not only has BCG-fibronectin binding been

demonstrated to occur at sites of disrupted urothelium, but this binding has also been demonstrated as necessary for the development of DTH and antitumor activity.

Summary

Though superficial bladder-cancer patients have been treated with intravesical BCG since 1976, the mechanisms of action remain unknown. Evidence points towards an immune mechanism of BCG-induced antitumor activity. Although specific antitumor immunity may play a role in BCG immunotherapy, additional work is needed to more clearly define this possibility. Several investigators have noted a clinical association between favorable response to BCG therapy and a systemic response (DTH) to BCG antigen, indicated by conversion to a positive purified protein derivative (PPD) skin test. Additional animal studies have, in turn, documented evidence of specific binding between BCG and fibronectin found in the urothelial basement membrane, which appears necessary for the development of both the DTH response and antitumor activity. Other studies have suggested which cellular components of the immune system and lymphokines may be involved in the antitumor response.

Further work will be needed to better understand BCG mechanisms, as these findings may be important to other forms of cancer therapy. Questions of immune suppression, genetic influence on the immune response, and immunocompetence at the time of surgery may assume increasing importance. A strong effort will therefore be needed to better understand these mechanisms so that patients may be selected, treated, and followed in a more effective manner.

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12. Adoptive immunotherapy of urologic tumors

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Introduction

The treatment of humans with advanced cancer represents a major therapeutic challenge. One approach to treating metastatic cancer is immunotherapy, which can be classified into active and passive categories. Active immunotherapy refers to the immunization of the tumor-bearing host with materials that attempt to induce in the host a state of immune responsiveness to the tumor. Passive (adoptive) immunotherapy involves the transfer to the tumor-bearing host of active immunologic reagents, such as cells with antitumor reactivity, that can mediate, either directly or indirectly, antitumor effects. Most attempts at immunotherapy in the last several decades have involved active immunotherapy utilizing nonspecific immune stimulators such as bacillus Calmette-Guerin (BCG), *Corneybacterium parvum*, and levamisole, with the hope that a nonspecific increase in human reactivity would concomitantly result in an augmentation of the putative antitumor immunologic response of the tumor-bearing host. The very large number of clinical trials of both specific and nonspecific active immunotherapy of human cancer performed in the last decade were almost universally unsuccessful, and enthusiasm for this approach to immunotherapy has waned considerably. Passive approaches to immunotherapy have been rarely utilized in the therapy of human cancer because of the theoretic and technical difficulties that were associated with raising the immunologic reagents necessary to perform these clinical trials. Recent developments in immunology and biotechnology have provided great impetus and opened new possibilities for the development of adoptive immunotherapies for the treatment of human cancer.

Development of adoptive immunotherapy as a practical cancer treatment required the following components:

1. Identification of immune lymphoid cells with a high degree of antitumor reactivity.
2. Techniques for expansion of these cells to large numbers (between 1×10^{11} and 5×10^{11} cells) sufficient for cancer treatment.
3. Generation of large amounts of recombinant lymphokines for in-vivo immunologic manipulations.

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The discovery of the T-cell growth factor (TCGF) interleukin-2 (IL-2) by Morgan, Ruscetti, and Gallo in 1976 [1] has enabled the generation and propagation large numbers of activated T lymphoid cells with antitumor reactivity. In 1983, Tanaguchi et al. isolated a human IL-2 complementary DNA (cDNA) clone from the Jurkat cell line and established its complete nucleotide sequence [2]. Soon thereafter Rosenberg et al. described the isolation of cDNA clones of the gene for IL-2 from the Jurkat cell line and from normal human PBL, their expression to high concentrations in *Escherichia coli*, and the purification of this recombinant IL-2 to homogeneity [3]. Thus use of recombinant DNA technology has provided a means for the production of large quantities of IL-2.

Interleukin-2 (IL-2)

IL-2 is a 15,000 dalton glycoprotein produced in minute quantities by helper T lymphoctes upon antigen or antigen-induced activation of resting T cells. Resting T lymphocytes do not secrete IL-2. However, the interaction between the human T-cell receptor and its ligand, in this case an antigen, in the presence of IL-1 (which is produced by macrophages) induces two events that are essential for proliferation of T cells. First, the interaction leads to expression of a gene, located on chromosome 10, encoding for the IL-2 receptor. Once the gene is activated, the message is then transcribed, the protein is translated, and the protein is placed on the cell membrane as a specific T-cell receptor for IL-2. In a similar fashion, the gene for IL-2, located on chromosome 4, is also activated de novo, resulting in the production of the lymphokine IL-2. It is that interaction between the IL-2 molecule and the specific high-affinity membrane receptor composed of a 55 kd alpha chain (Tac antigen) and a 75 kd beta chain on activated T cells that causes (initiates) T-cell proliferation, differentiation, and a wide variety of other immunoregulatory phenomena both in vivo and vitro [4]. In vivo, IL-2 has been shown to enhance natural killer (NK) cell function, augment alloantigen responsiveness, improve recovery of immune function in acquired immunodeficient states as well as in nude mice, and mediate regression of cancer in experimental animals and in selected patients with advanced cancer [5]. In addition, IL-2 administration has been shown to have direct effects on the endothelium, causing emigration of lymphoid cells from the peripheral blood into tissues, and to mediate the release of a variety of other lymphokines, including gamma interferon and other hormones such as adreno-corticotropin, cortisol, and growth hormone, each of which may mediate a number of effects [6, 7]. The ability to stimulate the in-vivo growth of T cells with antitumor reactivity appears to be an important part of the mechanism of IL-2 action.

A different role of IL-2, first described in our laboratory in 1980, involves the effect of IL-2 on non-T non-B lymphocytes. The incubation of resting lymphocytes in IL-2 for 3–4 days results in the generation of cells capable of

lysing a variety of fresh, NK-resistant tumor cells, but not normal cells, in short-term ^{51}Cr release assays. This phenomenon was termed *lymphokine activated killing* or *LAK* [5, 8–13].

IL-2 receptors have also been found on B cells and appear to play an important role in the proliferation and differentiation of a subset of activated B cells [14, 15]. Similarly, IL-2 receptors have been identified as macrophages, the significance of which is still unclear [16–18].

Immune lymphoid cells that can be used for adoptive immunotherapy

We have identified two types of immune lymphoid cells that can be obtained from murine and human tumor-bearing hosts and can be used for adoptive immunotherapy. One type of cell is the LAK cell, which can be easily generated in large numbers in both experimental animals and in humans.

The second subpopulation of lymphocytes, termed *tumor infiltrating lymphocytes* (TIL), appear to have a far greater efficacy than LAK cells in the treatment of experimental tumors [19]. TIL are lymphocytes infiltrating into growing tumors that can be isolated from these tumors by growing single cell suspensions of the tumor in IL-2. In this section we will review laboratory investigations concerning LAK cells and TIL populations.

Lymphokine activated killer (LAK) cells

In-vitro studies. Based on cell-surface phenotype, the spectrum and specificity of tumor lysis, and the responses to various BRM, LAK cells are believed to represent a lytic system distinct from that of NK cells and cytolytic T lymphocytes (CTL), although this is still an area of some controversy. The basic characteristic of LAK cells is their ability to lyse fresh, noncultured, NK-resistant, syngeneic or allogeneic, primary or metastatic cancer cells. Thus LAK cells are functionally distinct from both NK cells and classic CTLs [10]. NK cells lyse selected cultured cell lines and have little reactivity against fresh tumor-cell preparations. LAK cells can be readily generated from human PBL and from cells from the thymus, spleen, lymph node, bone marrow, and thoracic duct. LAK cells can be obtained from virtually all normal individuals and tumor-bearing patients [5]. Most fresh tumors are capable of being lysed by LAK cells [20]. We have recently demonstrated that RCC cells are highly sensitive to in-vitro killing by LAK cells. Thirteen of 13 different fresh renal tumor cell preparations tested in 57 experiments and two of two renal tumor lines tested in 10 experiments were all lysed by LAK cells. Renal-cell cancer (RCC) patients, like normal donors, generated good LAK effector cells with broad antitumor specificity against autologous tumors and a variety of allogeneic tumors. Fifty of 57 LAK effectors tested showed significant lytic activity (greater than two lytic units/10^6 cells) against fresh RCC targets [21].

The precursors of LAK cells appear to fall in the non-B, non T 'null' cell population and have now been identified as distinct from mature T-cell lymphocytes and monocytes: They are nonadherent, most are $T3^-$ (CD3, Leu4) and do not form rosettes with sheep erythrocytes (E rosettes) [22]. They bear Fc receptors for polymeric IgG (CD16, Leu11) and a complement (C_3bi) receptor (CD11, Leu15) [23]. Most LAK precursors and effectors in human peripheral blood lymphocytes were recently shown to be $Leu4^-$, $Leu19^+$, the phenotype of typical NK cells [24]. Highest LAK activity is present in the $Leu7^-$, $Leu11^+$, $Leu15^+$ fraction [25]. Following the administration of IL-2, LAK precursor cells ($CD16^+$, $CD11^+$, $CD3^-$) disappear from the peripheral circulation of patients after a single intravenous bolus of IL-2 [26]. In the mouse the precursor of the LAK cell effective in vivo was shown to be Thy-1^-, Ia^-, immunoglobulin$^-$, but asialo-GM-1^+ [27–29]. At the effector stage, cytotoxic cells are Thy-1^+, Ia^-, FcR^+.

In-vivo studies. Several animal models have been developed in our laboratory to test the immunotherapeutic efficacy of LAK cells in the treatment of established tumors [30]. Liver and lung micrometastases, from a variety of immunogenic and nonimmunogenic, 3-methylcholanthreneinduced sarcomas, the B16 melanoma, and the MCA-38 adenocarcinoma could be inhibited by treatment with a combination of LAK cells plus IL-2 (Fig. 1). While the

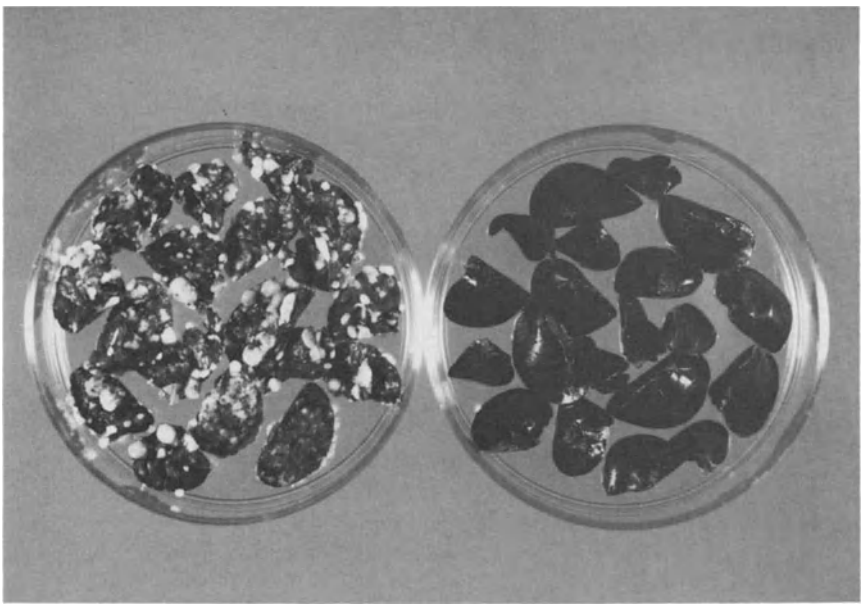


Figure 1. Representative lungs from four mice bearing 105 MCA metastases (experiment 8 in Table 2 in reference 31) from the group given Hank's balanced salt solution (HBSS) or LAK plus IL-2 (right).

administration of LAK cells alone could sometimes decrease the number of metastases, the addition of IL-2 greatly enhanced this effect [27, 31–36]. In these studies it was also shown that a direct relationship exists between the therapeutic effect and the administered does of IL-2 and LAK cells.

The mechanism of the therapeutic effect of LAK cells and IL-2 has been studied extensively in animals. It appears that the adoptively transferred LAK cells proliferate in vivo in a variety of host tissues under the stimulation of IL-2. The expanding LAK cells maintain their antitumor reactivity and are responsible for the antitumor effects. When IL-2 administration is discontinued, these lymphoid infiltrates resolve within a few days [37]. More recently, we have demonstrated that high-dose IL-2 alone is also effective in the inhibition of both micro- (3-day) or macro- (10-day) pulmonary metastasis. The administration, for example, of 100,000 I.P. of IL-2 three times daily to weakly immunogenic mice bearing 10-day established pulmonary metastases had a 79.5% reduction in the number of metastases, while mice receiving 20,000 to 50,000 U had a 22% reduction [33–35]. Studies have shown that high-dose IL-2 administration alone can lead to the generation of endogenous LAK cells in vivo. This responsiveness to high-dose IL-2 is in part also dictated by the immunogenicity of the tumor [38]. In murine models, there is a direct relationship between the amount of IL-2 that is administered and the extent of the antitumor effect. The amount of IL-2 that can be given is, however, limited by toxic side effects [39]. Attempts have therefore been made to find methods for generating cells with more potent antitumor reactivity and for reducing the requirement for the administration of high doses of IL-2.

Tumor-infiltrating lymphocytes (TIL)

Studies were undertaken to find tumor-specific T-lymphoid cells that could be used in the adoptive therapy of cancer [40]. TIL were since found to have a far greater efficacy than LAK cells when used for adoptive immunotherapy.

In-vitro studies. Data from various laboratories in the past indicated that freshly isolated TIL from a wide variety of human tumors demonstrate an immunologically depressed responsiveness compared with PBL or lymphnode lymphocytes, as measured by their proliferative and cytotoxic activity [41–47]. The underlying mechanism for the depressed activity of TIL is unknown, although the presence of suppressor cells [48], activation of suppressor cells by tumor-cell supernatants [49], production of suppressive factors by tumors [50], and depressed recycling capacity for multiple lytic events [45] have all been proposed as mechanisms. This suppressor activity, however, could be reversed by the addition of IL-2 [51]. IL-2 results in the *in vitro* expansion of activated T cells within the tumor, and as the lymphocytes expand they result in the destruction of surrounding tumor cells. By 2–3 weeks of culture, pure populations of lymphoid cells devoid of tumor cells are present. We have now

developed techniques for the isolation and expansion of TIL from human tumors, and TIL have been successfully grown from over 150 resected human cancers, including cancers of the kidney (RCC), colon, and breast; and melanoma; and sarcoma (Fig. 2) [52–56]. An example of one tumor cell suspension prepared by a 16-hour enzymatic digestion of a freshly resected RCC is shown in Figs. 3A and 3B. We have previously shown that the total number of cells required for human adoptive immunotherapy protocols can be reached by the in-vitro expansion of TIL, but often not for PBL. An average-size RCC will yield approximately 2×10^9 to 4×10^9 cells containing 1 to 2×10^9 lymphocytes (median of 55% lymphocytes). Three to four passages in vitro (approximately 18–22 days in culture) will suffice to bring the total number of lymphoid cells up to $2–3 \times 10^{11}$ cells [55]. Human TIL cells are quite different from LAK cells. Whereas LAK cells are derived from non-B, non-T lymphocytes, TILs are derived from T cells, and when expanded in culture they have the phenotype of classic cytolytic T lymphocytes [56]. Of great interest is the specificity that some human TIL have for their autologous tumors. Recent studies by Muul et al. [56] and Topalian et al. [57, 58] in our laboratory identified 3 of 6 and 4 of 14 different melanoma cultures with specific autologous antitumor reactivity, respectively. We, however, were unable to identify specific cytolytic responses in cultures from patients with RCC, including over 60 long-term TIL cultures [55, unpublished data] and six lines derived from required tumor-invaded, lymphnode lymphocytes (LNL) [59]. Similarly, nonspecific lytic activity has been seen with TIL isolated from

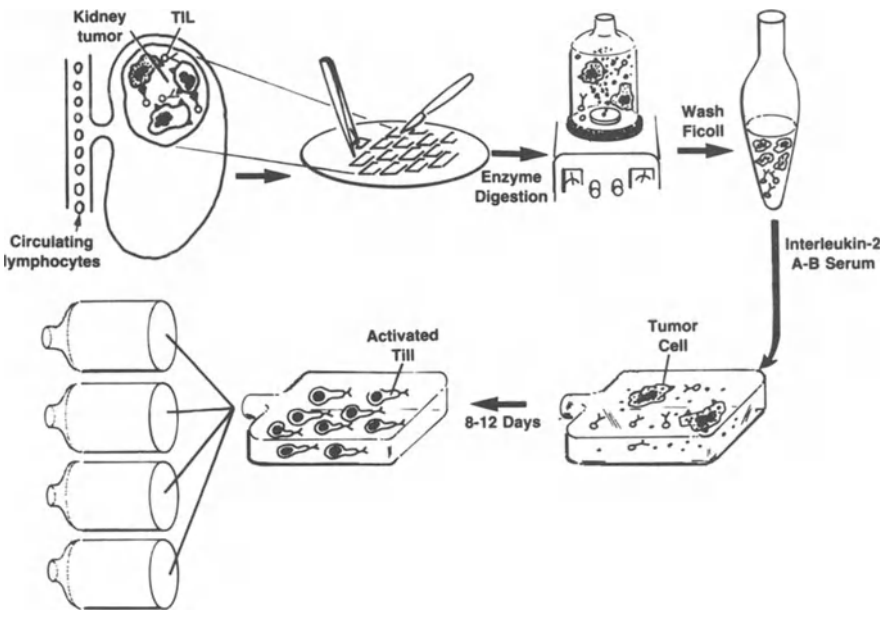
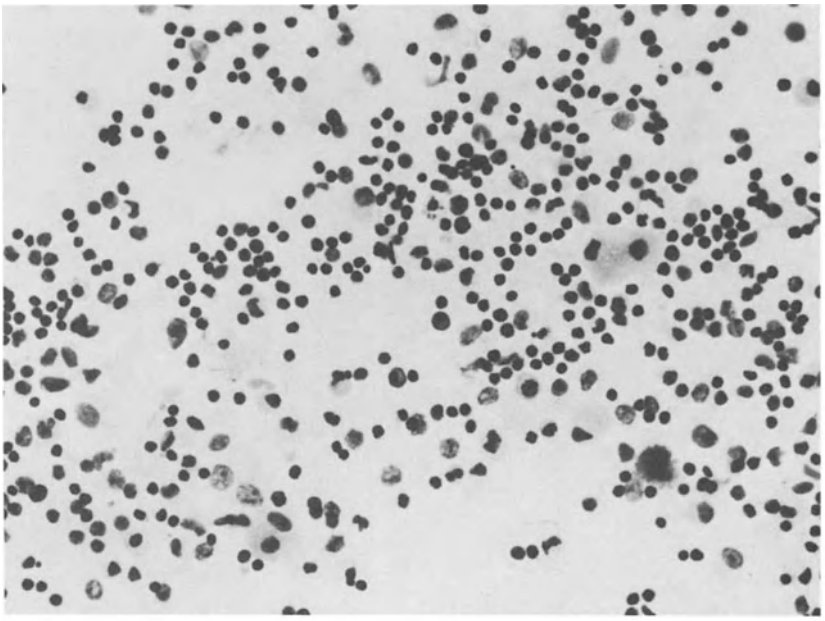
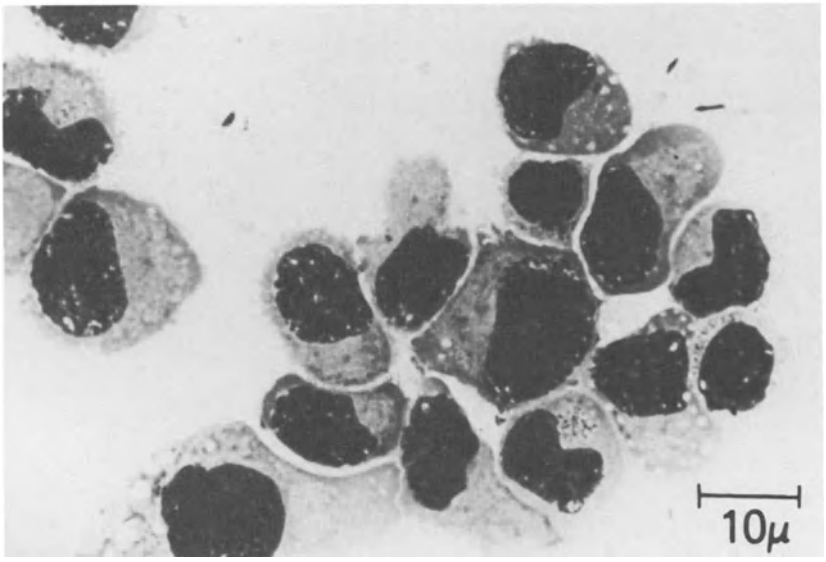


Figure 2. Technique of isolation and characterization of human tumor infiltrating lymphocytes.



A



B

Figure 3. A: Fresh tumor cell suspension from patient with renal cell cancer obtained by enzymatic digestion. Count of 200 cells revealed 75% lymphoid; 19% tumor cells, 6% plasma cells and histocytes. Tumor cells are characterized by enlarged nuclei. B: IL-2-activated tumor infiltrating lymphocyte culture derived from a patient with renal-cell cancer. The culture was maintained for 10 days in complete medium in the presence of 1000 units IL-2/ml. Note the activated shape of the lymphocytes in contrast to the unactivated state shown in Fig. 3A.

gastric carcinoma [60], lung carcinoma [61–64], squamous cell carcinoma of the head and neck [65], sarcoma [53], and breast, colon, esophageal, and brain tumors [66].

In-vivo murine studies. When TIL populations were studied in experimental tumor models, they exhibited far greater effectiveness than did LAK cells [19]. The adoptive transfer of TIL expanded in IL-2 to mice bearing pulmonary micrometastases (3-day) from various types of tumors showed that TIL are 50 to 100 times more effective in their therapeutic potency than are LAK cells [67]. When transferred in combination with IL-2 and cyclophosphamide, TIL were capable of eliminating large tumor burdens present in the liver and lungs of mice bearing a colon adenocarcinoma or sarcoma [19]. Large doses of TIL alone could exert antitumor effects against microscopic tumors independent of IL-2 administration, although combination therapy with IL-2 enhanced the effectiveness of TIL about fivefold. In contrast to the broad specificity of LAK cells, TIL isolated from some murine tumors and from some human melanomas demonstrated unique cytolytic specificity for the tumor from which they were derived and did not lyse allogeneic cancers or normal cells [19, 56–58]. Because of the greater potency of TIL compared to LAK cells and the ability to isolate specific cytolytic TIL from some human tumors, we have recently initiated clinical trials using TIL in the treatment of patients with advanced cancer.

Clinical studies using adoptive immunotherapy

The principles learned from our in-vitro and in-vivo studies described so far provided the basis for designing clinical trials testing the feasibility and efficacy of the administration of immune lymphoid cells to patients with advanced cancer. Figure 4 schematically describes two possible approaches to the adoptive immunotherapy of cancer.

Clinical studies with IL-2 and LAK cells

After having established the safety of administration of IL-2 and LAK cells independently to patients [5], studies were begun, in November 1984, combining the administration of IL-2 with LAK cells to patient with advanced malignancies who failed conventional therapy. The treatment regimens, results, and toxicities of therapy for our first 25 patients were initially reported in 1985 [68] and then extended to include 108 and 139 patients reported in 1987 and 1988, respectively [69, 70]. Our protocol for immunotherapy with LAK cells and IL-2 is shown in Fig. 5. All patients had evaluable disease, either by routine imaging studies or by physical examination. No patient received any therapy other than this immunotherapy for the 30 days

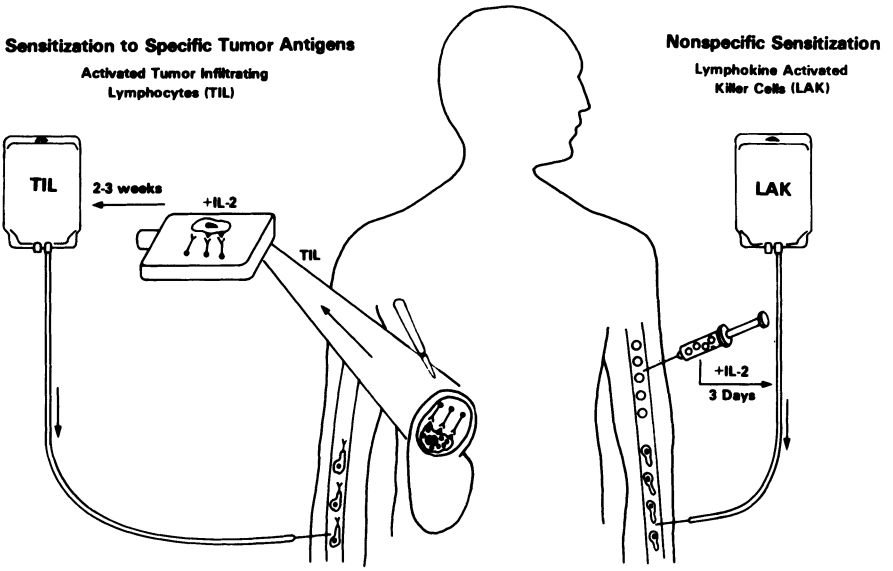


Figure 4. Two possible approaches to the adoptive immunotherapy of cancer.

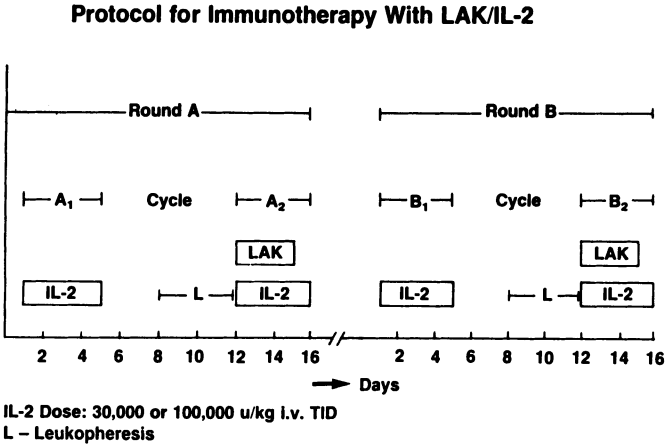


Figure 5. Protocol for immunotherapy with LAK and IL-2.

prior to treatment or throughout the follow-up period. Tumor regressions were seen in patients with RCC, melanoma, colorectal cancer, and non-Hodgkins lymphoma. The results of our clinical experience in the treatment of 222 patients with advanced cancer is shown in Table 1. Of the 137 evaluable patients, 12 patients experienced complete regression (CR) of all metastatic cancer and 17 patients had partial regressions (PR) (greater than

Table 1. Results of immunotherapy in patients with advanced cancer (accrued by 5/1/87 and assessed 7/1/87)

	LAK/IL-2			IL-2		
Diagnosis	Total evaluable[a]	CR (Number of patients)	PR	Total evaluable[b]	CR	PR
Renal	54	7	10	38	4	3
Melanoma	34	3	3	23	0	6
Colorectal	27	1	2	10	0	0
Non-Hogkin's lymphoma	4	1	2	3	0	0
Sarcoma	6	0	0	1	0	0
Lung adenocarcinoma	5	0	0	1	0	0
Breast	2	0	0	1	0	0
Brain	1	0	0	2	0	0
Esophageal	1	0	0	0	0	0
Hodgkins lymphoma	1	0	0	0	0	0
Ovarian	1	0	0	0	0	0
Testicular	1	0	0	0	0	0
Gastrinoma	1	0	0	0	0	0
Unknown primary	1	0	0	0	0	0
Total	137	12	17	80	4	9

[a] Two treated patients not included [one died of therapy (melanoma) and one lost to follow-up (breast)].
[b] Three treated patients not included [died of therapy (renal)].

50% reduction) of tumor. Regressions of tumors were seen in liver, lung, bone, subcutaneous tissue, skin, and circulating tumor cells. Fifty-four patients with RCC received LAK and IL-2 immunotherapy. Seven patients experienced CR and 10 patients had PR, for a total of 33% response (CR + PR).

Studies with IL-2 alone. Eighty evaluable patients received administration of high-dose bolus IL-2 alone. Four CR and 9 PR were observed in these patients [70]. Of 38 patients with RCC in this group, 4 CR and 3 PR were achieved, for a total (CR + PR) of 18.4%.

Of the 16 patients who were treated with either IL-2 alone or IL-2 + LAK cells and demonstrated a complete remission, 13 remain in complete remission from 3 to 31 months. The median duration of the 26 patients with partial remission is 6 months and eight of these patients are still responding at 6–20 months. Of note is the fact that as of October 1, 1987, we have treated a total of 315 cancer patients with 452 courses of high-dose IL-2, either alone or with LAK cells, and the clinical results have remained similar to those reported in the first 157 patients [71].

TIL immunotherapy

Clinical trials in the human testing of the therapeutic efficacy of TIL plus IL-2 in combination with cyclophosphamide in the treatment of humans with advanced cancer have just begun. Our phase I trials indicate that it is a feasible and practical protocol. Twelve patients, including six with melanoma, four with RCC, one with breast carcinoma, and one with colon carcinoma, were treated with varying doses and combinations of TIL (8.0×10^9 to 2.3×10^{11} cells per patient), IL-2 (10,000 to 100,000 u/kg three times daily to dose-limiting toxicity), and cyclophosphamide (up to 50 μg/kg). Two partial responses (PR) to therapy were observed in this pilot study: Pulmonary and mediastinal masses regressed in a patient with melanoma and a lymph node mass regressed in a patient with RCC. No toxic effects were directly attributable to TIL infusions [51]. A variety of efforts are currently underway to increase the therapeutic efficacy of treatment by increasing the number of TIL infused or by using different lymphokine combinations and automating cell production, hence reducing the complexity of treatment [39].

Toxicity of treatment

The toxicity of the administration of LAK + IL-2 immunotherapy is attributable to the use of high doses of IL-2. Administration of LAK cells alone to patients with cancer causes minimal side effects but also mediates no beneficial antitumor effects [72]. Most of the toxicity associated with this

therapy is related to a presumptive increase in capillary permeability, which leads to fluid retention, interstitial edema, and organ dysfunction (Fig. 6) [73]. Shortly after administration of IL-2 there is a profound drop in systemic vascular resistance with concomitant tachycardia, a decrease in mean arterial blood pressure, and an increase in cardiac index. As IL-2 administration continues, weight gain increases and urine output drops. The relative hypovolemia is easily treated with both crystalloid and colloid fluid replacement. The latter results in a weight increase and, as interstitial fluid accumulates in the lung, it leads to respiratory compromise and a decrease in arterial oxygenation. Vasopresesors are commonly used to minimize the need for fluid replcement [39]. Renal dysfunction is common, and more than 90% of the patients show some degree of acute renal dysfunction [74].

Details of the clinical course of two representative patients, demonstrating renal pathophysiologic responses to IL-2 administration, are shown in Fig. 7. Patient A, a 58-year-old female, received LAK/IL-2 therapy for an adenocarcinoma of the colon with extensive liver and retroperitoneal metastases. With initial administration of IL-2 (100,000 μ/kg IV every 8 hrs), a significant

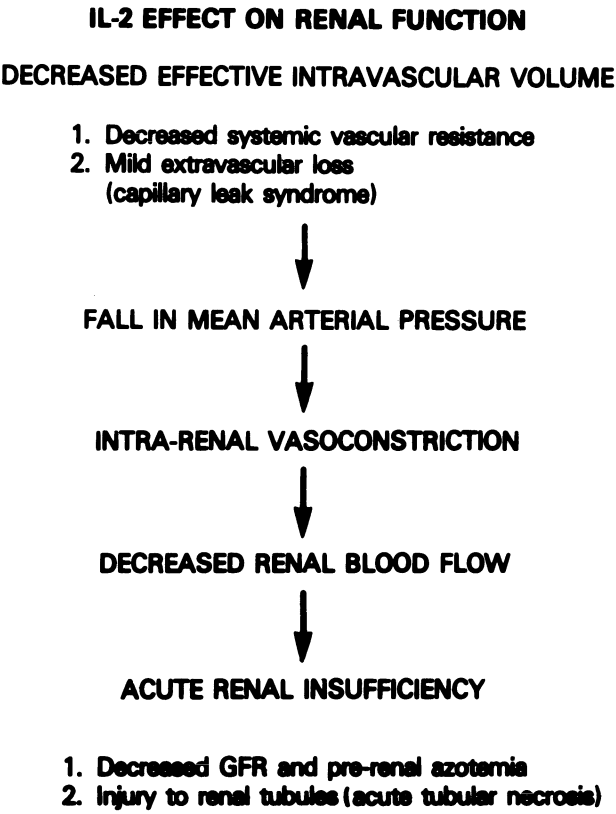


Figure 6. Pathophysiologic effects of IL-2 on renal function.

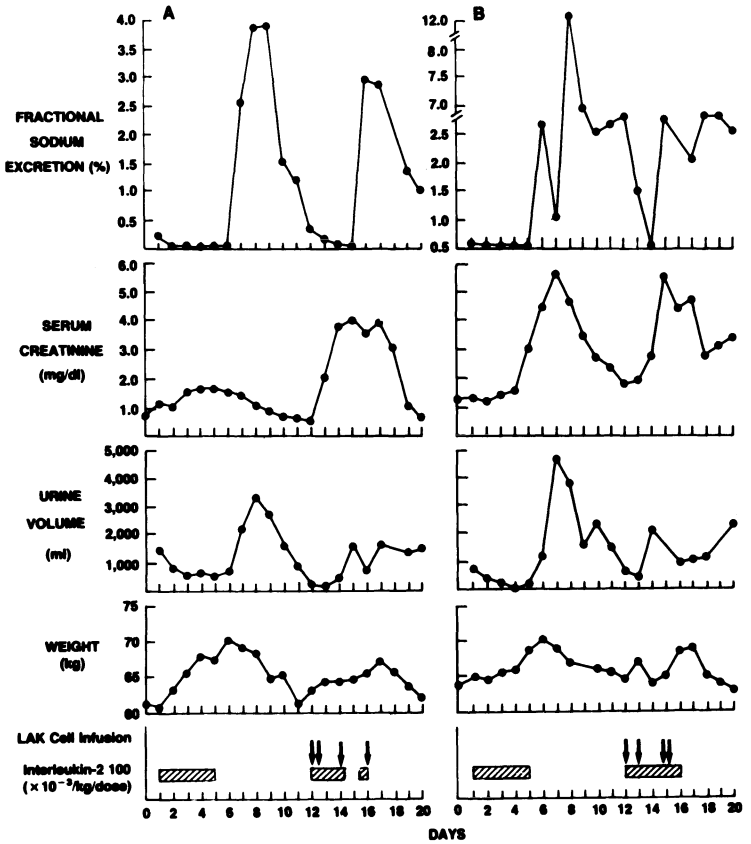


Figure 7. Effects of IL-2 on renal function in two representative patients with advanced cancer.

reduction in urine volume, a rise in serum creatinine, weight gain, and a drop in FeNa were observed; within 48 hours of IL-2 administration, daily urine volume dropped from 1467 ml to 589 ml, with a concomitant increase in serum creatinine from 0.8 to 1.5 mg/dl and in body weight from 61.8 to 65.3 kg. The FeNa levels dropped to 0.008%. After IL-2 administration was stopped, all levels returned to baseline. A similar pattern of a decrease in urine volume, an increase serum creatinine, weight gain, and a drop in FeNa was seen in the A_2 cycle when IL-2 was administered simultaneously with LAK cells (days 12–16), suggesting that these effects were manifestations of an IL-2-mediated, LAK cell-independent phenomenon. On day 14, urine volume was 353 ml, serum creatinine 3.8 mg/dl, body weight 65.0 kg, and FeNa 0.1%. The following day the patient became nauseated and confused, dyspneic and hypotensive, and required 2 days of pressor support (Dopamine and Neosynephrin). IL-2 doses were held on day 15 and the last dose was given on day 16. Daily examinations failed to reveal proteinuria, hemoglobinuria, or urine sediment abnormalities. The discontinuation of IL-2 resulted in an increase of FeNa to 2.8% on the same day.

All adverse effects disappeared promptly, and by day 20 urine volume and serum creatinine had returned to the pretherapy baseline levels. Excess weight was lost by day 21, when the patient was discharged for follow-up. Furosemide was given on days 4, 5, 7, 8, 13, and 15. The FeNa remained low following diuretic therapy on days 4 and 13.

Patient B, a 29-year-old male with widespread metastatic renal-cell carcinoma to lung, supraclavicular, and regional retroperitoneal lymph nodes underwent a left radical nephrectomy 2 months prior to initiation of LAK/IL-2 therapy. The patient's initial response to IL-2 administration was similar to that observed in patient A, with a significant drop in daily urine volume (to 257 ml), an increase in weight (5 kg over baseline), and serum creatinine (3.1 versus 1.3 mg/dl pretherapy level), and a drop in FeNa to 0.02%. After discontinuation of IL-2, an increase in FeNa occurred, reaching 5.6% and 12.3% on days 6 and 8, respectively. Furosemide was administered on days 7 and 8, and therefore was not the cause of the increase in FeNa observed on day 6. In contrast to patient A, however, upon termination of IL-2 in cycle A_1, serum creatinine continued to rise, reaching a peak of 5.6 mg/dl on day 7, and broad granular casts were seen in the urine sediment, compatible with acute tubular necrosis (ATN). Subsequently, a very gradual decrease in serum creatinine was observed, which had not returned to baseline level by day 12 (1.7 versus baseline of 1.3 mg/dl) when administration of IL-2 simultaneously with LAK cells was begun. During the course of the A_2 cycle, the patient developed fever (39°C), chills, nausea, vomiting, lethargy with hypotension, tachycardia (>180 beats/min), and dyspnea. Fluid retention was noted with peripheral edema and ascites. He was placed on vasopressors and received furosemide IV on days 14, 15, and 16 (150, 100, and 100 mg/day, respectively). Upon termination of therapy, all adverse effects disappeared promptly, except for a slow decrease in serum creatinine, which returned from its peak to the pretherapy baseline value of 1.3 mg/dl 29 days later. The patient was discharged 4 days after discontinuation of IL-2 in stable condition.

The changes in serum creatinine levels, urine volume, body weight, and fractional excretion of sodium in our first 99 patients treated with IL-2 are shown in Fig. 8. IL-2 therapy was associated with moderate degrees of azotemia (median, 3.1 mg/dl; range 1.0–12.6), acute weight gain (median, 9.4%; range 2.4–27.2%), oliguria (median 471 ml), and markedly decreased fractional sodium excretion (median, 0.042%, range 0.0001–0.399%), all supporting a preherapy acute renal failure as the basis for the renal dysfunction [75]. As with virtually all of the other side effects of IL-2, these changes were transient, and all patients returned to baseline creatinine levels with a median time of 4 days for a return to normal. Two factors, pretherapy (baseline) serum creatinine levels and previous nephrectomy, were associated with the severity of the changes in renal function and with a significantly prolonged recovery [74, 76].

Other toxicities in these patients included hepatic dysfunction (hyperbiliru-

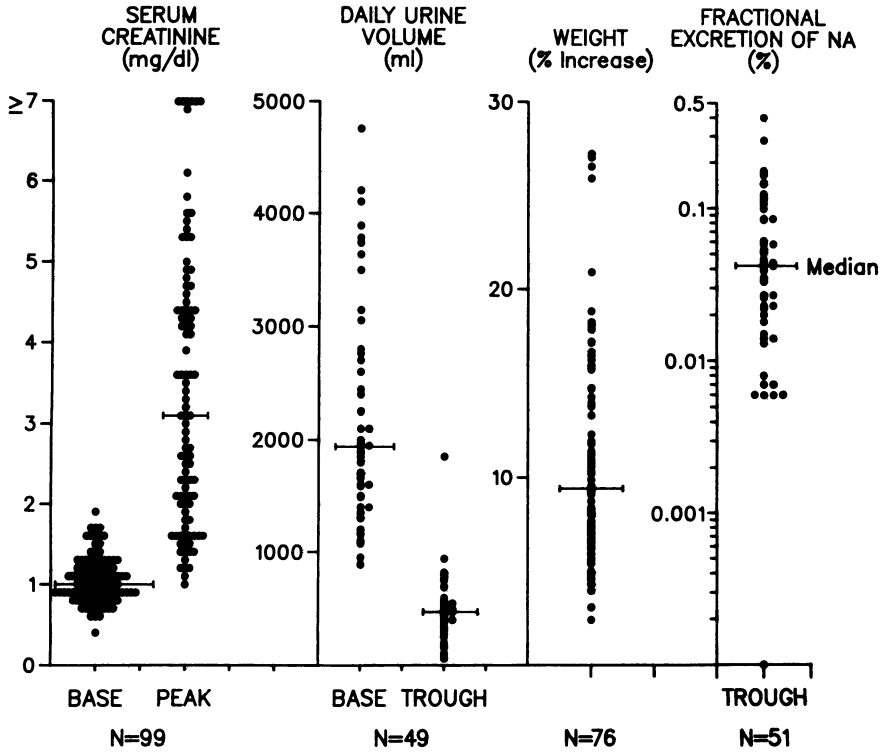


Figure 8. Changes in renal function induced by IL-2 in patients receiving immunotherapy for advanced cancer.

binemia), hematologic abnormalities (anemia, thrombocytopenia), nausea, vomiting, and confusion. These side effects promptly reverse after IL-2 administration [77, 78]. Analyses of several of these toxicities of treatment have been reported elsewhere [39]. Five of the 222 patients have died of treatmentrelated complications. The median treatment course lasted 16 days, and the median time from the end of treatment to discharge from the hospital was 5 days.

Several groups have more recently suggested that the continuous infusion of low-dose IL-2 causes less toxicity than bolus administration [79–80]. With a maximum dose of 50,000 μ/kg/24 hours, Wang et al. observed minimal toxicity and only mild degrees of renal insufficiency, suggesting that the antitumor effects and the toxic effect of increased vascular permeability might be dissociated.

Combination chemoimmunotherapy

Adoptive immunotherapy is an approach that can ideally be combined with chemotherapy, radiation therapy, or any of the new biologic response

modifiers. Several combinations of chemotherapeutic agents with IL-2 were tested in our laboratory in mice bearing advanced pulmonary tumors. A synergistic effect was found between cyclophosphamide and IL-2 [81], possibly based on the elimination of tumor-induced suppressor cells and/or by direct tumoricidal activity. Of interest is the fact that in these studies chemotherapy with cyclophosphamide appeared to derease the toxicity associated with IL-2 therapy. Mitchell et al. have recently reported on a regimen of low-dose cyclophosphamide and low-dose IL-2 administered in an outpatient setting to 27 patients with advanced melanoma. Tumor regression was noted in liver, lung, subcutaneous, and lymph node metastases. Most patients were able to go home within and hour after IL-2 infusion was administered [82].

A different combination of chemoimmunotherapy in a murine model was also reported by Salup and Wiltrout. Mice bearing established Ren Ca (RCC) tumors received a combination of doxorubicin hydrochloride and IL-2-stimulated cytotoxic lymphocytes plus IL-2, resulting in the cure of 67% of the mice [83]. Many patients, however, do not respond to immunotherapy, and major efforts are needed to improve and increase the effectiveness of these approaches, to abrogate the toxicity, and to lessen the complexity of treatment. Recently, immunotherapy with combination cytokines has emerged as a promising approach and is currently being studied in murine models as well as in humans. Various combinations of lymphokines, such as IL-2 and tumor necrosis factor (TNF) [84], TNF and gamma-interferon [85], or IL-2 with alpha-interferon [86], have shown substantial antitumor synergies and have enabled reduction of the doses necessary to achieve these therapeutic effects. A summary of other clinical immunotherapy studies now in progress in the Surgery Branch of the National Cancer Institute is shown in Table 2. It

Table 2. Clinical immunotherapy trials in progress in the Surgery Branch, National Cancer Institute

1. Prospective randomized trials
   a. Advanced cancer
      i) IL-2 alone
      ii) IL-2 plus LAK cells
2. Monoclonal antibody plus IL-2 in patients with advanced colorectal cancer
3. Chemotherapy (5-FU plus leucovorin) plus IL-2 in patients with advanced breast and colorectal cancer
4. Tumor infiltrating lymphocytes plus IL-2 (plus cyclophosphamide) in patients with advanced cancer
5. Evaluation of new cytokines and combinations of cytokines
   a. Tumor necrosis factor (TNF) plus IL-2
   b. Alpha-interferon plus IL-2
   c. Granulocyte-macrophage colony stimulating factor (GM-CSF) alone or with cyclophamide

is hoped that these immunological approaches can be further improved and developed into clinically applicable strategies for treating cancer patients.

Conclusions and future prospects

In this chapter, we have described the development of a new approach to the treatment of cancer based on the administration of high-dose IL-2, either alone or in conjunction with the adoptive transfer of immune lymphoid cells (LAK cells or TIL). Although the efficacy of this form of treatment for selected patients with advanced cancer has been established, much needs to be learned before successful adoptive immunotherapy for human cancer is a practical clinical reality. For the present time, it is a promising experimental form of therapy.

The studies reviewed here have demonstrated for the first time that immunologic manipulations of the tumor-bearing host can affect the growth of established cancer and that some patients with cancer can in fact mount immunologic responses against their own growing malignancies.

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