BENIGN PROSTATIC HYPERPLASIA

Part of "32 - BENIGN PROSTATIC HYPERPLASIA"

Urinary obstruction as a result of benign prostatic disease has probably been recognized to some degree since the earliest days of medicine. This association was probably first formalized by Riolan in the seventeenth century. In the mideighteenth century, Morgagni (248) provided one of the earliest descriptions of BPH and enumerated many of the potential medical problems attendant to its development. More exact recognition of the pathologic process has been credited to Virchow in the last quarter of the nineteenth century. Since then, information regarding the incidence, gross and histologic characteristics, biochemical composition, associated pathologic and physiologic changes, and pathophysiologic effects of BPH has increased markedly. However, despite increased understanding of normal prostate growth, identification of the cause of BPH remains elusive.

Incidence

Autopsy studies have repeatedly demonstrated an association of BPH and aging based on histologic criteria, calculated or actual prostate weight, or prostate volume. For example, Randall (292) found that histologic evidence of definite or probable BPH exceeded 50% in men over 50 years of age and rose to 75% as men entered the eighth decade. Age-related autopsy prevalence of histologic BPH is

similar in several countries despite differing racial mixes (Fig. 32.18) (167). On the other hand, clinically important mass-producing BPH occurs in only about half (40% to 50%) of men with presumed histologic BPH and is clinically manifested in about half of these (167). Its reported clinical incidence varies appreciably in different parts of the world (83). Based on the combined data from ten autopsy studies, Berry and associates (27) constructed curves for the prevalence of BPH with age (Fig. 32.19). Their analysis implies that BPH is probably initiated before age 30. Their calculated doubling time for BPH weight varies with age, being 4.5 years in the 31- to 50-year age group, 10 years in the 51- to 70-year age group, and more than 100 years in the 70+-year age group. The observed increased mean prostate weight of glands requiring surgical intervention compared to that of glands with hyperplasia recognized at autopsy reinforces the potential role of prostate mass in BPH voiding dysfunction suggested in the Olmsted County–based male voiding pattern studies (117).

FIGURE 32.18. Age-specific prevalence of histologic benign prostatic hyperplasia *(BPH)* in various geographic male populations. (From Isaacs JT, Coffey DS. Etiology and disease process of benign prostatic hyperplasia. *Prostate* 1989[Suppl 2];33, with permission.)

The clinical literature available on racial and regional incidence of BPH and its impact on individuals is difficult to interpret critically (83,218). The reported data include observations

of clinical and pathologic phenomena that use different sampling and evaluation criteria (273), making exact comparisons difficult. Nevertheless, these studies clearly indicate an increasing but quantitatively variable incidence of pathologic or clinical BPH with aging. They suggest that black and white populations in the United States have a similar incidence of BPH, although development of symptoms probably occurs earlier in blacks (71). Blacks in the United States seem to have a higher prevalence of adenomatous hyperplasia than blacks on the African continent. Data from the first half of the twentieth century indicated a much lower prevalence of BPH in native Chinese and Japanese than in white populations (273,311). Data from recent mass screening evaluations in Japan reported a 9.9% and 11.6% prevalence of BPH in men 70 to 79 years of age and 80 years of age and older, respectively (273), reaffirming this impression. Evaluation of the racial background of patients subjected to prostatectomy in Hawaii indicated a relatively diminished requirement for prostatectomy in Chinese and Japanese as compared with white males. However, a series of recent observations suggests that environmental rather than racial or genetic factors play a significant and probably major role in these observed differences in incidence and prevalence of BPH. In a series of 321 unselected autopsies from the Beijing and Shanghai districts of China between 1989 and 1992, more than 30% of the 95 men older than 40 years of age showed evidence of BPH (137a). A study of BPH in rural and urban males revealed a similar prevalence of this benign growth in the urban but not rural Chinese population; dietary differences were thought to play a significant role in this observation (137a). In addition, the increased identification by ultrasound examination of nodular BPH with age (51% in 70- to 79-year-olds) in a community-based study in Shimamaki, Japan (226), as well as the increased prevalence of evidence of BPH in men with Asian ancestry in Hawaii and San Francisco (83,92) compared with native Japanese, seems to relegate race and genetic factors to a limited role in prevalence of clinical BPH. Prospective ultrasound evaluation of monozygotic and dizygotic twins (241), coupled with historical assessments of twins (279) and families with a high incidence of prostatectomy in men younger than 64 years of age (316), supports possible genetic factors in development of BPH. As the result of their twin studies, Meikle and colleagues (241) suggested that hereditary factors substantially contribute to symptomatology but that nongenetic factors have more influence on zonal volumes of the prostate. Overall, the clinical and pathologic observations suggest little racial or genetic influence on the prevalence of histologic BPH but a significant probability that environment,

possibly dietary intake, and possibly genetic factors in a limited patient cohort may influence the rate and degree of development of mass-producing BPH.

Pathology

BPH in humans is a nodular, regional growth with a variegated gross appearance resulting from the inhomogeneous and irregular mixture of glandular and stromal tissue. Although BPH nodules may arise in the peripheral prostate, they are almost always located centrally in the periurethral portion of the enlarged gland (Fig. 32.20). BPH develops in a variety of gross configurations and periurethral sites, resulting in various anatomic designations such as median lobe, median bar, and lateral lobe hyperplasia. Randall (292) observed eight gross anatomic configurations: lateral; posterior commissural or median; lateral and

median; subcervical (Albarrán's lobe); lateral and subcervical; anterior commissural; subtrigonal (lobe of Home); and lateral, median, and subcervical lobes (Table 32.1). Bilateral or middle lobe involvement was identified in approximately 59% of Randall's cases. In many instances, the nodular hyperplasia is

P.1419

separated by a distinct, smooth, cleavage plane from the compressed peripheral prostate that resembles a capsule. The weight of the hyperplastic tissue is highly variable, ranging from a few grams to more than 200 g; no clear relationship between the size of the adenoma and the degree of bladder neck obstruction has been established.

FIGURE 32.20. Transverse section of adult prostate with benign prostatic hyperplasia. The nodular, variegated structure of the periurethral adenomatous tissue is evident. The compressed peripheral prostatic tissue (“surgical capsule”) is evident.

TABLE 32.1. INCIDENCE OF TYPES OF LABOR HYPERTROPHY

Observation of the hyperplastic prostate with light microscopy confirms the variable findings suggested by the gross appearance. All the glandular and stromal elements of the normal prostate are involved to a variable degree by hyperplasia. Franks (100) identified five types of nodules based on their histologic characteristics: (a) stromal (fibrous or fibrovascular), (b) fibromuscular, (c) muscular (“leiomyoma”), (d) fibroadenoma, and (e) fibromyoadenoma. He pointed out that true stromal nodules were found only in the subepithelial tissue of the urethra (Fig. 32.21,Fig. 32.22 and Fig. 32.23). Moore (247) emphasized that they arose in the lateral walls of the urethra, well removed from the utricle. He also stated that small stromal nodules were present in every enlarged prostate. Commonly, large nodules are fibromyoadenomas. Glandular elements in the nodule vary a great deal. Acini may be large or small, with some cystic changes. Epithelial cells may be tall-columnar, cuboidal, or flattened low-cuboidal in configuration; they may be arranged peripherally, show papillary infolding, or assume a cribriform pattern (Fig. 32.24). Both ductal and acinar epithelium appear

P.1420

to be involved in the proliferative process. The acini may have epithelium similar to normal mature glands, except perhaps with more papillary extensions (active), or they may have an inactive prepubertal type of appearance (inactive). Transition zones and buds of proliferating epithelium showing spindle-cell metaplasia are also seen. A number of histologic variants of BPH, including postatrophy, basal cell, cribriform, and atypical adenomatous hyperplasia, as well as sclerosing adenomas and stromal hyperplasia with giant cells, have been recognized. At times, differentiation of these variants from carcinoma can be difficult (32). Franks (101) stated that the ultrastructural appearance of the hyperplastic gland reflects the characteristics noted on light microscopy. Although several observers have reported prominent intercellular lacunae in BPH (Fig. 32.25), critical differences between the cells of the normal and hyperplastic gland have not been

identified. Acute and chronic inflammatory changes are common in association with hyperplasia. Interestingly, careful examination reveals that even well-defined nodules almost always merge with the surrounding tissue at some point.

FIGURE 32.21. Transverse section of human prostate gland demonstrating small focal nodules of predominantly stromal hyperplasia. Their modest size and periurethral location are characteristic. Also note concomitant glandular hyperplasia. (From Mostofi FK, Price EB. *Tumors of the male genital system,* series 2, fascicle 8, *Atlas of tumor pathology.* Washington, DC: Armed Forces Institute of Pathology, 1973, with permission.)

FIGURE 32.22. Stromal hyperplasia. This represents a higher magnification (×10) of the stromal nodules demonstrated in Fig. 32.21. Again, note the close proximity of the urethral lumen. (From Mostofi FK, Price EB. *Tumors of the male genital system,* series 2, fascicle 8, *Atlas of tumor pathology.* Washington, DC: Armed Forces Institute of Pathology, 1973, with permission.)

FIGURE 32.23. Stromal hyperplasia (×115). In benign prostatic hyperplasia (BPH), the fibromuscular stroma is often found to loosely envelop adjacent hyperplastic acini or occasionally form discrete compact nodules. In distinction to the hyperplastic process found in breast, the fibromuscular stroma in BPH lacks excessive amounts of elastic tissue. (From Mostofi FK, Price EB. *Tumors of the male genital system,* series 2, fascicle 8, *Atlas of tumor pathology.* Washington, DC: Armed Forces Institute of Pathology, 1973, with permission.)

FIGURE 32.24. A: Photomicrograph (×80) of a focus of predominantly glandular hyperplasia. Note occasional papillary infolding, the two-cell layer composition of the acini, and the abundance of surrounding and intervening stromal elements. **B:** Higher-magnification view (×300) better demonstrating the consistent presence of basal and adluminal cell components to the individual acini, as well as the loose intervening stromal component. Adluminal papillary proliferation is well demonstrated. (From Mostofi FK, Price EB. *Tumors of the male genital system,* series 2, fascicle 8, *Atlas of tumor pathology.* Washington, DC: Armed Forces Institute of Pathology, 1973, with permission.)

FIGURE 32.25. Electron micrograph of epithelial cells in benign prostatic hyperplasia (×7,000). No distinct ultrastructural differences are noted between normal and hyperplastic prostatic epithelial cells except occasionally prominent intercellular lacunae *(L).* Prominent basement membrane *(BM)* and subadjacent collagen bundles are noted. (From Fisher ER, Jeffrey W. Ultrastructure of human normal and neoplastic prostate with comments relative to prostatic effects of hormonal stimulation in the rabbit. *Am J Clin Pathol* 1965;44:119, with permission.)

Associated Pathology

Infarction of the prostate, thought to occur predominantly in prostates of substantial size exhibiting nodular hyperplasia (1,16,247), is said to be present in approximately 25% of large glands. Acute massive prostatic infarction has been observed in association with septic shock, hemorrhagic shock caused by a ruptured abdominal aortic aneurysm, coronary artery bypass, repair of aortic and iliac artery aneurysms, and pyonephrosis (93). Infarcts vary in size from tiny to 5-cm lesions and are commonly located periurethrally. A speckled, grayish-yellow appearance occasionally associated with hemorrhagic streaks and a sharply delineated, often hemorrhagic periphery are characteristic. Spiro and associates (338) noted prostatic infarction in 85% of the glands in patients with and in 3% of those without acute urinary retention. Others have found no definite or a lesser predominance of identifiable infarction in patients treated for acute retention (8). Prostatic infarcts may be associated with significant elevation of the serum prostate markers (308). Histologically, infarcted areas reveal centrally located coagulation necrosis with hemorrhagic changes in the peripheral margins. Metaplasia of adjacent ductal and acinar epithelium often results in a squamous or transitional epithelial configuration (252). Although acini involved with metaplasia (308) may lack the characteristic basal cell layer, all the cells involved are typically well differentiated and demonstrate no evidence of anaplasia or invasion that would be expected with malignancy.

Prostatic calculi have been recognized with an incidence varying from 7% in prostate pathology specimens to 20% at autopsy, 30% in radiologic studies, and even higher incidence on ultrasound evaluation (128). The calculi have either a lobular or polyfaceted laminar surface (371). Based on their composition, they have been classified as primary, forming inside the acinus, or secondary, forming within the prostatic ducts. Primary calculi characteristically have a nucleus of apatite with concentric layers of apatite and whitlockite. Peripheral layers of whewellite and occasionally weddellite may be present. These calculi may be completely crystalline or have areas with a sizable amount of organic material, or a nucleus suggesting an amylaceous body. Secondary calculi may have a nucleus of whewellite or uric acid (290). Classically, the calculi are deposited within the cleavage line that exists between the nodular hyperplasia and the surgical capsule. On routine radiographs, true prostatic calculi appear as scattered calcifications overlying the pubic symphysis and the superior pubic rami. Multiple clustered calculi may be recognized on rectal examination by characteristic

crepitation. Single calculi have a firmness on rectal examination suggestive of carcinoma.

Two lesions that warrant discussion because of their resemblance to or association with BPH are papillary adenoma of the utricle (aberrant prostatic tissue) and blue nevus of the prostate. Aberrant prostate tissue may involve the utricle, the base and perimeter of the verumontanum, or the entire prostatic urethra. These lesions tend to occur in younger men, manifest clinically most often with gross painless hematuria, and are indistinguishable from adenomatous hyperplasia of the prostate (252). Postmortem specimens suggest that these lesions usually represent a hyperplastic proliferation of normal tissue.

Blue nevus of the prostate may be associated with prostatic hyperplasia and cause confusion with malignant melanoma. Histologically, this lesion is characterized by infiltration of the prostatic stroma by clumps of spindle-shaped cells containing a granular

brown, iron-negative, bleachable, Fontana-Masson–stained pigment within their cytoplasm (252).

Biochemical Characteristics

The concentration and content of steroids, enzymes, minerals, and a variety of compounds have been determined in the hyperplastic tissue and compared with normal and carcinomatous tissue. Identification of normal tissue and preservation of its biochemical characteristics for analysis is a problem that requires persistent attention. The variable composition of tissue samples of BPH and carcinoma as demonstrated on histologic study undoubtedly increases the challenge to obtain consistent results in their analysis. Nevertheless, a sizable body of information regarding steroid content, metabolism, and specific binding, as well as other biochemical characteristics of normal and pathologic prostate tissue, has been published in the past 30 years. As analytic techniques have improved, a significant portion of these data have been modified or discarded. The following seems a reasonable summary of the current state of our knowledge.

The observations (90) that dihydrotestosterone and androstenediol are the principal metabolites of radioactive testosterone incubated with human BPH tissue *in vitro* have been adequately confirmed. However, reports that BPH tissue has a higher concentration of DHT than normal or peripheral prostate have not been supported in repeated assessments of appropriately preserved surgical tissue. In these specimens, BPH and peripheral prostate had similar tissue levels of DHT (5.0 and 5.1 ng/g) and testosterone (1.8 and 1.2 ng/g) (373). These findings were eventually confirmed by Bartsch and colleagues (21) and Norman and colleagues (266). A weak correlation was observed between DHT concentration and the content of glandular tissue. Bartsch and colleagues (21) reported low levels of progesterone, estrone, estradiol, and estriol (0.02 to 0.06 ng/g tissue) in surgically removed BPH and normal prostate tissue from kidney donors. In contrast, Krieg and associates (191) found markedly increased estradiol (6.2 versus 2.2 fmol/mg protein) and estrone (7.4 versus 0.9 fmol/ng protein) levels in mechanically separated stroma from suprapubic prostatectomy specimens compared with prostate tissue from six brain-dead 21- to 61-year-old kidney donors. DHT and T concentrations in stroma were similar in surgical and kidney donor specimens but were reduced in prostate epithelium from kidney donors. Normal tissue levels of DHT in BPH tissue seem paradoxic in view of the decreased serum testosterone levels in aging men (125,370); the increased 5α-reductase activity of BPH stroma could partially account for this finding (36) but seems unlikely to do so.

Evidence that 5α-reductase activity is increased two to three times in BPH (35,162,166) and is predominantly localized to the stroma is substantial. Prostatic tissue obtained from 50 men subjected to open prostatectomy and 15 brain-dead organ donors 14 to 38 years of age had 6 to

15 times greater 5α-reductase activity in the crudely separated stroma than did the epithelium regardless of the histology of the prostate (36). These observations suggest that the relatively increased amount of stromal tissue in BPH as compared with normal tissue may contribute significantly to its (BPH) reported increased 5α-reductase activity. Availability of an antibody to 5α-reductase type 2, the isoenzyme present in prostatic

tissue, has permitted immunohistochemical evaluation of a variety of tissues for this enzyme. Limited observations demonstrate perinuclear staining of basal and stromal cells in normal and BPH tissue. The predominant staining in BPH as contrasted with “normal” prostate was in the stroma rather than basal cells (332,333). No 5α-reductase antigen was detected in luminar epithelial cells.

Attempts to characterize, localize, and quantify steroid receptors in BPH as compared with those in normal or peripheral prostatic tissue have been persistent. The gene for the androgen receptor has been cloned and sequenced, and its protein product has been characterized (48,58), adding sophisticated tools to study this aspect of androgen effect on cells. With immunohistochemical techniques (225,245) the physiologically important androgen receptor is localized in the nucleus. Evidence suggests that nuclear androgen receptor content is increased in BPH compared with peripheral prostate (59). The presence of estrogen receptors in the prostate has now been confirmed by most investigators. In general, estrogen-binding sites are reported to be more numerous in stroma than in epithelial cells and to be decreased in concentration in BPH as compared with normal tissue (59,77,180,321). Interest in the role of estrogen receptors has been increased by the isolation of a second estrogen receptor in the rat prostate and confirmation of its presence in human prostate (49). Progesterone receptors are also present in appreciable concentrations in the cytosol of prostatic epithelial cells; the concentration in BPH is significantly greater than that in normal tissue (21). However, progesterone receptors have not been identified in the nucleus of prostatic cells. Although the receptor–steroid complexes clearly have significant roles in the growth and function of prostatic cells, the exact mechanisms involved and the significance of receptor data with regard to the development and growth of BPH are still unclear.

Enzymes

Evaluation of the concentration of a series of enzymes involved in steroid metabolism in BPH as compared with normal or peripheral prostate in addition to the previously discussed 5α-reductase has not provided insightful information. Observations of significantly decreased 3α- and 3β-hydroxysteroid oxidoreductase reductase and 17β-hydroxysteroid oxidoreductase oxidase activities in surgically removed BPH compared with surgically removed normal prostate (166), changes favoring increased DHT formation in BPH, were not confirmed later by the same group (34). Brendler and colleagues (34) reported a three to six times higher acid phosphatase activity in BPH than in peripheral prostatic tissue. The activity of several other cytoplasmic enzymes, including alkaline phosphatase and lactic dehydrogenase, did not differ in BPH and normal tissue. Histochemical studies have demonstrated marked β-glucuronidase and *N*-acetyl-β-glucosaminidase activity in the prostatic epithelium of BPH (265) and of aminopeptidase in normal prostate and BPH (185). However, aminopeptidase activity was diminished or absent in some BPH nodules (185) and was decreased in concentration in tissue homogenates compared with normal tissue (264). Histochemical staining revealed no difference for a group of oxidative enzymes in BPH and normal prostate tissue (264). Interestingly, staining for glucose-6-phosphate dehydrogenase and β-hydroxybutyrate dehydrogenase activity was almost absent and weak, respectively. Nonspecific esterase and succinic dehydrogenase staining were similar

in normal and hyperplastic prostate.

Organic Compounds and Metal Ions

BPH has a high concentration of citric, lactic, and aconitic acids per gram of tissue, but accurate comparisons with the concentrations found in normal tissue are not available. No α-ketoglutaric or succinic acid was detected in BPH (335). Zinc content has variously been reported to be elevated (141) and identical (142) to the high level noted in normal prostatic tissue. Cadmium has been reported to be present in much higher concentration in BPH than in normal tissue (142). Magnesium has been shown to be increased in concentration in the epithelial cells of BPH by histochemical studies and in the tissue by atomic absorption spectrophotometry (141).

Summary of Biochemical Aspects of Benign Prostatic Hyperplasia

As indicated, despite extensive and continuing efforts, no qualitative differences in steroid content or metabolism, enzyme activity, organic compounds, or metal ions have been documented between BPH tissue and either normal prostatic tissue or the peripheral prostate from a gland with BPH. The few quantitative differences in biochemical characteristics reported require confirmation and have not helped identify a unique aspect of the metabolic activity characterizing BPH.

Natural History of Anatomic Benign Prostatic Hyperplasia

The first pathologic evidence of BPH occurs in less than 10% of the men in the 31- to 40-year-old group (Table 32.2). This observation may indicate that the initiating

factor is present in most men of this age, with its effect being recognizable only in a few, or that young men with recognizable BPH have a discrepancy between physiologic and chronologic aging. Evidence of histologic and anatomic BPH increases with age; by the ninth decade the former is identifiable in approximately 90% and the latter in probably over half of men (150). The initial lesion of BPH almost always occurs in the periurethral area proximal to the verumontanum. Although descriptions of the ductal and glandular structure of this area vary, it is generally agreed that BPH arises from an inner set of prostatic ducts and glands that reside within the urethral wall or adjacent to it. McNeal (235) designates the paraurethral portion of this tissue the transition zone; it composes approximately 5% of the normal gland. The histologic characteristics of the earliest BPH lesions are probably variable. Those that develop within the urethral wall are usually composed of a mass of loose embryonic-appearing stroma devoid of glands; however, glandular tissue predominates in early lesions developing in the transition zone (234). McNeal (235) and Franks (101) agree with the latter's statement that stromal and epithelial hyperplasia may occur alone or together. Once the process is initiated, all elements of the normal prostate—stromal and glandular—participate to a variable degree in its progression. The glands in the hyperplastic nodules seem to have the capacity to bud and form new ducts and acini; in contrast to normal tissue, these new glandular elements grow toward each other. Pure stromal nodules rarely reach large size. The variable local response to a postulated

inductive agent is evident from the nodular nature of the BPH. Not all the nodules of BPH are in the same phase of development, as is clearly indicated by Moore's observation (247) that small stromal nodules were present in every enlarged prostate. This observation does not preclude the possibility that BPH results from a sequence of initiating and promoting effects that are episodic. Both the average weights of the prostate and the incidence of prostatectomy by decade suggest that once BPH has developed, it is progressive in most men. The rate of growth calculated by Berry and colleagues (27) indicates a prolongation of the doubling time with age. The important question of whether established BPH ever stabilizes or regresses spontaneously cannot be evaluated from the information available. Based solely on clinical criteria, many authors, including ourselves, are of the opinion that both occur (see also Natural History of Benign Prostatic Hyperplasia Voiding Dysfunction).

TABLE 32.2. AGE PREVALENCE OF HUMAN BENIGN PROSTATIC HYPERPLASIA (BPH)

Etiology

Identifying the etiology of BPH has been a continuing challenge. The universal regional development of histologic BPH (167) in aging men with testes that produce an androgen-diminished environment (125) is an as yet unexplained paradox that is independent of race and environment. The subsequent development of mass-producing BPH is selective (166) and seems potentially to be related to a variety of factors, at least some of which are associated with environment and lifestyle. In proposing etiologic factors in this common benign growth in humans, the unusual pathologic features of BPH including nodular growth and stromal predominance require consideration in addition to its characteristic periurethral localization. Over time, neoplastic, inflammatory, metabolic and nutritional, vascular, racial, and a variety of other etiologic factors have been considered as causes of BPH (251). Newly identified systemic or local prostatic growth-promoting agents traditionally receive prompt consideration. Evidence has been presented suggesting a genetic factor in a small group of men developing BPH. Currently, four hypotheses regarding the etiology of BPH are prominent: the DHT or altered hormone environment

hypothesis, the embryonic reawakening hypothesis (236), the stem cell hypothesis (167), and the nonandrogenic testis secretory factor hypothesis (129,133). Two of these, the embryonic reawakening and the stem cell hypotheses, focus on intrinsic cellular phenomena. The embryonic reawakening theory proposes that the interaction between glandular tissue of prostatic origin and stroma related to the bladder produces a reawakening of embryonic inductive interactions resulting in tissue with growth characteristics that lead to the development of BPH (236). Subsequent growth of BPH is postulated to be multifactorial (197,277), with altered hormone environment and stromal epithelial interaction having varying degrees of prominence in this phenomenon. The stem cell hypothesis proposes an increase in prostate stem cell number and that of the amplifying and transient cells derived from them as the basic phenomenon leading to the development of BPH. Neither the embryonic reawakening nor the stem cell hypothesis proposes an identifiable inducing mechanism to initiate or sustain the phenomena

proposed.

The so-called DHT hypothesis, perhaps more appropriately termed the *altered hormonal environment* hypothesis, and the nonandrogenic testis secretory factor hypothesis center on alterations in testis secretory function or changes in local or systemic hormone metabolism with age that may initiate or sustain phenomena leading to the development of BPH. Several studies demonstrate that with aging the male human develops an androgen-diminished environment. This decrease in systemic androgen is accompanied by stable or possibly slightly altered systemic estrogen and increased steroid hormone binding serum levels (125,137,255). The latter further decreases the biologically available systemic testosterone. Although DHT and androgen receptor (AR) concentrations in BPH tissue are high, they do not differ from peripheral or normal prostate levels. The evidence suggests that androgens are necessary for but not sufficient to induce development of BPH. Estrogens have demonstrated physiologic effects on male accessory sex gland growth, including the prostate in animals (224); this primarily involves the stromal tissue (171). BPH can be induced in the dog by coadministration of androstanediol and estrogen (277,375). The recent discovery of a second estrogen receptor, estrogen receptor-β (ERβ), has stimulated additional speculation about potential mechanisms for and role of estrogen in prostate BPH growth. Of interest, genistein and other phytoestrogens have a much higher affinity for ERβ than ERα (49). However, despite the appreciable information from animal experimentation, and human tissue and serum hormone analysis with aging in men, the role of estrogen in the development and progression of BPH remains controversial. Attempts to correlate serum hormone levels with benign prostate pathology in radical prostatectomy specimens (278) and with ultrasound-assessed prostate size and anatomic configuration in twins (241) and longitudinal evaluation of serum hormone levels and manifestations of BPH (108) have also failed to provide insights into its etiology. Excluding the possible significant effects of estrogen imprinting on the neonatal prostate (288), these data suggest that estrogen may share a potential role in BPH mass development with a variety of other variously derived agents. Overall, the multiple studies of changes in known steroid hormone secretory products of the testis have not provided a highly probable explanation for the critical role of the testis in the development and growth of BPH in humans.

The nonandrogenic testis factor (NATF) hypothesis proposes that the testes secrete a nonandrogenic prostate growth-stimulating factor, almost certainly a protein, that plays a critical role in the ubiquitous development of histologic BPH and possibly a contributory role in the subsequent development of mass-producing BPH (129,133,165). Biologic evidence supporting the presence of a nonandrogenic male accessory sex gland growth-stimulating substance in the aging male human was derived from assessment of age-related changes in the concentration of selected prostate and seminal vesicle secretory products and seminal vesicle weight (126,130). The testes were targeted as a source of this hypothesized prostate growth-stimulating agent based on the evidence that neither endogenous nor exogenous testosterone or estradiol could replace a normally functioning testis in producing BPH in dogs (131,176) and evidence for a systemic prostate growth-stimulating substance that was not a steroid in the testis-intact but not the castrated rat. Evaluation of possible secretion of a nonandrogenic prostate stromal cell stimulating protein by the testis (NATF) was carried out using stimulation of the proliferative response

of human prostate stromal cells to testicular epididymal plasma derived from human spermatoceles (STEP) *in vitro* as evidence for its existence. Exposure to STEP produced both androgen-independent and androgen-synergistic stromal growth stimulation repeatedly in this system (133). Isolation and identification of the protein (NATF) responsible for this stimulation is progressing. Animal studies indicate that the prostate is exposed to NATF by a systemic delivery route; in addition, the presence of NATF in the testosterone-rich testicular epididymal plasma fosters potential exposure of periurethral prostatic tissue to these independent and synergistic prostate growth-stimulating compounds. We postulate that this exposure induces the almost universal periurethrally localized development of histologic BPH. Subsequent selective stimulation of prostatic mass is postulated to be induced by multiple factors with a significant but less well defined role for exposure to systemic or local NATF.

Pathophysiology

Concepts regarding the etiology of urinary symptoms and sequelae resulting from BPH traditionally focused on the development and progression of mechanical obstruction

P.1425

from the prostatic mass as the cause. The perception that the mass and configuration of the hyperplasia dictated the degree of outflow blockage undoubtedly resulted from the early experiences in treatment of patients with acute and chronic urinary retention. Renal failure, urinary tract infection, and calculi were common indications for various approaches to relieve bladder neck obstruction. The commonly observed reversal of these serious secondary phenomena and restoration of normal or markedly improved voiding patterns reinforced the mass-obstruction concept. Failures in both of these therapeutic goals were overshadowed by the frequent correction of the various significant problems that existed. Absence of a direct correlation between the size of the prostate and presence or degree of obstruction was recognized as indicated by the designation “prostatism sans prostate” or the admonition “small prostate, big residual.” If functional results of mass removal were less than optimal, the concept of probable persistence of mechanical obstruction was pursued by determining postvoid residual urine to evaluate bladder emptying, carrying out endoscopic reassessment of the lower urinary tract primarily to assess the possibility of persistent mass, and at times performing a simple urodynamic evaluation. Proposals implicating intrinsic prostatic tension from contracting prostate stromal smooth muscle (43,198) or extrinsic tension on the BPH prostate mass by a contracting or contracted prostate capsule (164,272) have been proposed as potentially having important roles in primary or persistent bladder outlet obstruction. The proposed role of stromal smooth muscle–mediated increased intrinsic prostate tension has been reinforced substantially by *in vitro* physiologic and to a lesser degree clinical observations with α-adrenergic agonists and receptor blocker agents, respectively (198). The proposed role of peripheral capsular tension on bladder outlet obstruction is supported by the results of transurethral incision (230,239) and impressively by the report of anterior commissurotomy carried out by Shafik (326). Although α-adrenergic agonist mechanisms may potentially affect voiding in a variety of ways that may complement the effects of BPH (198), these secondary phenomena seem unlikely to play a direct role in the primary BPH-mediated effects on voiding.

BPH-mediated bladder outlet obstruction results in a series of changes in bladder tissue

mass, composition, and function; it also affects blood supply and nerve status and function. Although not well documented, it seems probable that the functional status of each of these physiologically important components of the bladder moderates its response to outlet obstruction. Nevertheless, the degree and persistence of the obstruction is thought to play a pivotal role in the resulting anatomic and functional bladder effects. The sequence of obstruction-induced pathophysiologic changes is variable, multifocal, and incompletely characterized (206,229). In humans, outlet obstruction can be the primary cause of physiologic changes varying from hyperfunction and hyperirritability to nonfunction or atony. Evaluation of this spectrum of functional states is difficult and confusing. Consequently, evidence of bladder changes associated with well-characterized bladder outflow obstruction is derived largely from observations in animals; the resulting observations probably are but may not be transferable to humans. In general, partial bladder obstruction results initially in a detrusor muscle hypertrophy and increased bladder weight that are reversible (206,229). Typically, increased muscle mass is associated with increased intravesical pressure on voiding (54). Studies in obstructed pigs demonstrate a decrease in functional bladder capacity, increased residual urine, detrusor instability associated with incontinence, and a prolonged period of hypoperfusion and associated tissue hypoxia (206), a sequence of physiologic changes that seem probable in humans. The human and the pig usually develop a thickened trabeculated bladder in response to outflow obstruction. However, the likelihood that a stable, balanced outlet obstruction or detrusor functional status and response state will be maintained if achieved seems problematic. Chronic retention of urine can lead to a thin-walled, flaccid bladder in the bladder outlet obstructed pig just as it does in some humans. In addition to impaired emptying, persistent obstruction is associated with increased collagen deposition and decreased compliance in humans (229). Rabbits with bladder outlet obstruction (229) develop a change in detrusor muscle myosin phenotype suggesting a trend to a dedifferentiated phenotype.

The varying mixes of anatomic and physiologic alterations described in response to obstruction probably play a major role in the specific bladder and renal changes that occur in individual patients. Currently, loss of bladder compliance is probably the major factor in producing upper urinary tract functional and anatomic damage. The etiology of the involuntary obstruction-related bladder contractions (319) remains problematic, but *in vitro* studies with isolated detrusor muscle from the obstructed pig bladder suggest that they have a myogenic, not neurogenic, basis (206). Fortunately, these involuntary contractions are reversible in clinical practice and animal models with relief of obstruction. Cellules, saccules, and diverticula are recognized and related anatomic bladder changes with potential clinical significance that develop and progress unpredictably. Based on their extensive experience with the pathophysiology of bladder obstruction induced bladder changes, Levin and colleagues (206) suggest that bladder outlet obstruction should be relieved as soon as possible after diagnosis to maximize the chance for bladder recovery.

Clinical Evaluation

Clinical evaluation to assess the presence and degree of voiding dysfunction or the role of BPH in its presence has an increasingly broad spectrum of potential goals. These include providing information for a range of epidemiologic

studies, selecting patients for drug or interventional studies, and providing information and advice to individual patients. The specific goal often plays a significant role in the character and extent of a patient's evaluation. The discussion of clinical evaluation that follows focuses on the management of the individual patient.

The goals of the clinical evaluation of the individual with voiding dysfunction caused by BPH are to identify the patient's voiding or, more appropriately, urinary tract problems, both symptomatic and physiologic; to establish the etiologic role of BPH in these problems; to evaluate the necessity for and probability of success and risks of various therapeutic approaches to these problems; and to present the results of these assessments to the patient so he can make an informed decision about management recommendations and available alternatives. The clinical evaluation centers on an evaluation of symptoms, physical findings, and results of laboratory and selected imaging and endoscopic studies.

Symptoms

Most patients with medical problems caused by BPH have symptoms of dysfunctional voiding. This symptom complex is nonspecific and is identified by many eponyms, including the currently favored nonspecific term *lower urinary tract symptoms* (LUTS) and the traditional term *prostatism,* implying an established etiologic relationship. We prefer the term *BPH voiding dysfunction* once the etiologic relationship with the prostate warrants serious consideration. As emphasized by Blaivis (31), the clinically recognizable bladder response to various stresses or pathologic changes can be the result of overactive (frequency, nocturia, urgency, urge incontinence) or underactive (hesitancy, intermittency, weak stream, urinary retention) detrusor activity. Blaivis (31) states that BPH symptoms are essentially caused by prostatic obstruction-induced impaired detrusor contractility, detrusor instability, or sensory urgency. They have multiple potential causes varying from those primarily associated with the lower urinary tract to systemic diseases (Table 32.3). The symptoms can be associated with primary diseases of the bladder, neurogenic and metabolic disorders, a variety of diseases of the cardiovascular renal system, use of pharmacologic agents (including antihistamines and antidepressants), markedly increased or abnormal fluid intake, and apparently also normal aging. A small group of patients with “silent prostatism” have severe physiologic sequelae of BPH-induced bladder neck obstruction such as bladder atony or renal failure with minimal or no voiding problems.

TABLE 32.3. DIFFERENTIAL DIAGNOSIS OF BENIGN PROSTATIC HYPERTROPHY

Separation of lower urinary tract symptoms into those related to voiding (delivery) and storage seems reasonable (172). Voiding symptoms include the following: hesitancy, a delay in initiating micturition; intermittency, an involuntary interruption of voiding; weak urinary stream; straining to void; sensation of incomplete emptying; and terminal dribbling. Of these symptoms, the prevalence of a weak urinary stream correlated with increasing age. The storage symptoms include the following: frequency, normal (longer than 3 hours) and abnormal (less than 2 hours); nocturia, awakening to void; urgency, an increasingly

strong desire to void; incontinence (urge, stress, overflow, anatomic); and bladder pain (pain in pelvis without voiding) or dysuria (pain and discomfort with voiding). Of these storage symptoms, nocturia, urgency, urgency incontinence, and frequency correlated with increasing age. Jepsen and Bruskewitz's review (172) of prevalence of bother from lower urinary tract symptoms indicated that nocturia was the most bothersome and urgency the second most bothersome urinary symptom, confirming a long-standing urologic dictum. Frequency was judged to have an intermediate bother level. This assessment of symptom bother probably provides a rationale for a difference in symptomatology between patients seeking medical care and those discovered by screening or recruitment. In either circumstance, using knowledge of the patient's perceived or elicited problems to direct thoughtful initial inquiry into the character and circumstances of voiding dysfunction is essential. Selectively supplementing this information with a voiding diary and knowledge of habits regarding food and fluid intake, sleep patterns, medication history, and so on can be invaluable in

directing appropriate diagnostic and therapeutic approaches in patients in whom BPH-induced voiding dysfunction is suspected.

Patients with BPH-induced bladder outlet obstruction may have complications of this problem, including acute urinary retention, manifestations of chronic urinary retention such as overflow incontinence or renal failure, or urinary tract infection. Acute urinary retention is signaled by the sudden onset of a persistent ineffectual urge to void and severe unremitting bladder pain. Retention may be precipitated early in the course of BPH voiding dysfunction by ingestion of decongestants containing an α-adrenergic agonist, antihistamines, or a variety of medications with parasympatholytic properties, including disopyramide (Norpace), tricyclic antidepressants, and numerous tranquilizers (380). Its occurrence postoperatively is well recognized. A retention episode may also be precipitated by a forced and prolonged delay in voiding, by a precipitous increase in urinary output caused by ingestion of ethanol or diuretics, and possibly by chilling.

Persistent or chronic urinary retention may manifest its presence by producing overflow incontinence or renal failure. Patients with a decompensated bladder caused by BPH-induced bladder neck obstruction may have problems of constant dribbling (overflow) incontinence accompanied by evidence of a persistently distended urinary bladder. Similarly, laboratory or clinical manifestations of renal failure may be the initial evidence of a significant upper tract effect of lower urinary tract obstruction. Both constant dribbling incontinence and renal failure have several potential etiologies. However, the possibility of lower urinary tract obstruction as the cause is easily evaluated and warrants consideration even in the absence of preceding or concurrent typical symptoms.

BPH bladder outlet obstruction–induced urinary stasis and accompanying bladder stones or diverticula may predispose to development of urinary tract infection. The predominance of symptoms such as dysuria, stranguria, urgency, and other irritative voiding symptoms often delays consideration of the role of BPH-induced abnormalities in development of the infection. Again, awareness of this possibility and of other diseases that produce similar symptom complexes is essential to minimize clinical diagnostic errors (Table 32.3).

BPH is the most common cause of gross hematuria in men older than 60 years of age.

Usually, hematuria from BPH is “initial” or “terminal,” but it can manifest as a significant bleeding problem requiring catheter placement or other acute intervention. Carcinoma of the prostate rarely manifests in this manner.

Symptom Indexes

The construction and use of symptom indexes to evaluate patients with bladder outlet obstruction caused by BPH has escalated. An increasingly scientific approach to target and evaluate appropriate symptoms resulted in the American Urological Association (AUA) symptom index in 1992. Development of this index was preceded by the Boyarsky symptom index, the Madsen-Iversen index, and the Maine Medical Assessment index; an International Prostate Score questionnaire and other assessment tools have been developed essentially concomitantly with the AUA symptom index. The indexes target questions that reflect changes in symptoms; they are not meant to be used as diagnostic screening instruments for BPH or bladder outlet obstruction. Several studies failed to document strong correlations between the AUA symptom index and anatomic and physiologic measurement of BPH effects (18,19,274). Despite the shortcomings indicated, the symptom indexes are recommended and used to compare results of research protocols and are recommended for the initial patient evaluation in an office setting (274) by U.S. and international guidelines. They are also used routinely in drug and interventional protocol studies. Many, including ourselves, have found the AUA symptom indexes to have a limited role in daily practice (173). One of us (KTM) uses them to confirm components of the history and quantify changes in response to treatment.

Physical Examination

The physical examination should be systematic and meticulous; it should be appropriately expanded based on history or observed physical abnormalities. The patient's general appearance and specific externally apparent abnormalities should be noted. The abdomen and genitalia should be examined by inspection, palpation, and appropriate percussion to identify any organomegaly, asymmetry, tenderness, or mass. Ordinarily, the bladder must contain at least 150 mL fluid to allow its detection by percussion; a residual urine in excess of 500 mL will usually produce a visibly distended bladder (44). Eliciting a sense of urgency by suprapubic pressure tends to confirm the nature of the identified mass. Ultrasound provides a noninvasive procedure to clarify the nature of a lower abdominal mass. Visual evidence of marked urethral meatal stenosis or recognition of a urethral or paraurethral mass on palpation may guide further appropriate evaluation.

A properly performed rectal examination provides essential information in evaluating patients with voiding dysfunction. In the male, the genitourinary aspects of the examination are usually enhanced by examining the supported, bent-over patient from behind. After inspecting the anal area, the rectal sphincter tone, noted on inserting the examining finger, provides evidence of the functional status of the somatic, sensory, and motor components of the sacral reflex arc and indirect evidence of parasympathetic input to the lower urinary tract (253). A thorough examination of the rectum, including the sacral hollow, may identify unsuspected

rectal pathology. During examination of the prostate, its size, consistency, and the integrity of its landmarks (median furrow, lateral sulci) should be noted and recorded.

Enlargement of the prostate may be manifested by increases in its normal width (4.4 cm), length (3.4 cm), or thickness. A universally accepted nomenclature describing prostatic size is not available. Perhaps an estimation of dimensions (width, length, vertical prominence) in centimeters constitutes the most reproducible form of assessment. A conventional paradigm for assessing prostatic size involves a grading scale ranging from normal through 4+. A normal gland (approximately 20 g) is about the size of a chestnut and is minimally perceptible on rectal examination. A 1+ enlarged prostate (about 25 g) is about the size of a plum and occupies a bit less than one-fourth of the rectal lumen. A 2+ enlarged gland (about 50 g) is about the size of a lemon and fills somewhat less than half of the rectal lumen. A 3+ enlarged prostate (about 75 g) attains the size of an orange and fills approximately three-fourths of the rectal diameter. A 4+ gland (100 g) may attain the size of a small grapefruit and fill so much of the rectal lumen that adequate examination is difficult. Digital assessment risks failing to recognize the presence or size of an enlarged prostate. On the other hand, a positive recognition of prostate enlargement is almost always confirmed. The consistency and symmetry of the prostate and presence, character, and location of nodules and induration (slight, moderate, stony), particularly with regard to distorting or compromising the median furrow and lateral sulci, should be noted. Crepitation should be recorded, if present. Palpable identification of the normally nonpalpable seminal vesicles or bladder base requires identification of a cause. After anatomic assessment of the prostate, massage should be performed unless acute prostatitis is suspected. Gentle rolling pressure with the examining finger from a lateral to a medial direction, progressing from the prostate base to the apex on each side, followed by stripping of the urethra distally usually produces fluid at the urethral meatus. The fluid should be retrieved on a slide and examined microscopically. Cultures of the expressed fluid directly or in a small volume of voided urine should be considered.

Laboratory Evaluation

Additional tests may aid in formulating the final clinical impression and treatment plan. These include blood and urine analyses, urodynamic evaluation, selected radiologic and ultrasound imaging studies, and cystourethroscopy. Their complexity, risk, and cost affect their selective employment. The urine should be tested for glucose, protein, occult blood, and pH with a multiparameter dipstick, ideally complemented by gross inspection and microscopic analysis of an initial (10 to 30 mL) and midstream sample of a freshly voided urine specimen. Urine culture, localization studies, and urinary cytology warrant selective considerations.

Blood studies may be desirable at the initial evaluation. A complete blood count (CBC), including differential count and gross assessment of platelet number, and a multiparameter chemical profile, including the guideline-recommended serum creatinine, warrant consideration. A careful history and physical examination will usually identify patients at risk for bleeding tendencies. In fact, the best screening test for disorders of hemostasis in surgical patients is a carefully acquired history soliciting examples of bleeding tendencies in the patient and in close relatives (64). In the absence of clinical evidence of a

hemostatic disorder, there is only a 0.008% probability that a given patient will have non–drug-induced intraoperative clotting disorders (82,346). Obviously, all surgical candidates should be questioned regarding their use of aspirin, nonsteroidal antiinflammatory drugs, and other agents capable of altering normal hemostasis. The determination of the absolute platelet count, bleeding time, and partial thromboplastin time (PTT) constitutes a reasonable screening procedure to verify clinical suspicions (45). Although controversial (302), the serum PSA level is commonly determined in men in the BPH age group, preferably before the rectal examination.

A urodynamic evaluation tailored to provide critical diagnostic information with the least risk, discomfort, and cost deserves consideration. Residual urine and urine flow rates can be determined noninvasively. An ultrasound assessment of postvoid residual urine in a patient who has been instructed to empty his bladder is the most common urodynamic study performed in our group; the patient is then asked to void again and the void volume also recorded. The postvoid residual has traditionally been used to assess bladder function, to guide diagnostic inquiry, and to evaluate efficacy of treatment efforts. Recently, these roles, particularly with regard to the evaluation of treatment efficacy, have been challenged because of numerically variable residual urine determinations, a feature shared with most urodynamic and other complex physiologic indicators. This failure to determine residual urine volume and use this information with judgment is a questionable practice, especially with the availability of ultrasound to measure volume. The Olmsted County study clearly demonstrates that most men in all age groups empty their bladder with less than 12 mL of residual urine. Approximately 20% of men in each decade from 40 to 80 had residuals of greater than 50 mL. Presence of BPH was disproportionally represented in this group. Men with a postvoid residual greater than 50 mL had a threefold increased risk of developing acute retention (188). These considerations, along with the evidence suggesting that residual urine volume measurements are at least as reproducible as other urodynamic determinations (302), deserve increased emphasis in evaluating the potential clinical roles of residual urine determinations. Maximum flow rate, flow pattern, and volume voided provide important information (see Chapter 26B). Voided volumes less than 150 mL or more than 500 mL provide suspect information.

P.1429

Review of the available literature indicated that prevalence of urine volumes greater than 200 mL varied with age (4). Data regarding flow rate determination indicate the following (302):

1. A significant variability (most, 1 standard deviation; half, 2 standard deviations) in repetitiously performed individual flow rates
2. A definite tendency toward substantially increased flow rate with sequential determinations
3. An appreciable decrease in maximum flow rate with age with 69% of 75- to 79-year-old men in the Olmsted County study below 15 mL per second and 35% below 10 mL per second

The evidence supporting the use of a peak flow rate of less than 15 mL per second to select patients for therapeutic trials of presumed BPH voiding dysfunction seems challengeable, as does the presumed advantage of flow rate over residual urine measurements. Simultaneous pressure-flow studies appropriately supplemented by video assessments provide the maximum opportunity to differentiate detrusor and outlet effects and have largely replaced the use of the cytometrogram. Data from initial and particularly repetitious urodynamic studies can provide very useful diagnostic and therapeutic insights.

In the past, evaluation of the upper urinary tract by radiologic or ultrasound imaging was commonplace in patients with bladder neck obstruction. Now these assessments are done selectively in patients with a history, physical findings, or laboratory studies that suggest a significant possibility of an important independent or secondary urinary tract abnormality accompanying the bladder outlet obstruction.

Cystourethroscopy to confirm the presence and effect of bladder neck obstruction from BPH is commonly done with local anesthesia in an outpatient setting. The presence, configuration, and site of obstructive tissue can usually be identified, but not its physiologic effect. The latter can be assessed to some degree by determination of residual urine and recognition of the presence and degree of trabeculation (Fig. 32.26) and bladder pathology such as diverticula and stones. Prostate size can be estimated crudely from the increase in length of the prostatic urethra, the degree and length of the adenomatous occlusion, posterolateral and anterior clefting present, and the thickness of the prostate when palpated rectally with the cystoscope in place.

FIGURE 32.26. Grading of bladder wall trabeculation. Tight, compact detrusor muscle bundles ultimately show evidence of hypertrophy and splaying of fibers (grade 1) with the gradual demonstration of multifocal cellules (grade 2) to small diverticula (grade 3). These changes appear to correlate with elevation of opening urethral pressure (degree of obstruction), as well as associated detrusor reflex instability. (From Andersen JT, Nordling J. Relation of prostatic lobes to degree and rate of obstruction. In: Hinman F Jr, ed. *Benign prostatic hypertrophy.* New York: Springer-Verlag, 1983, with permission.)

Rectal or abdominal ultrasound may be used to assess prostatic size and weight with accuracy to within 5%. An assessment of residual urine and possibly the thickness and configuration of the bladder wall may provide some supportive evidence for bladder neck obstruction (5,336). Computed tomography and magnetic resonance imaging studies can provide information with regard to prostatic size, but, again, not its physiologic significance; they are rarely indicated to assess BPH and its associated voiding dysfunction.

Cystography and retrograde and voiding urethrography can at times provide invaluable information with regard to the diagnosis and evaluation of bladder or urethral diverticula. These studies warrant consideration in patients with clinical evidence of bladder neck obstruction who have an unusual course or unexplained findings.

Natural History of Benign Prostatic Hyperplasia Voiding

Dysfunction

Data regarding clinically important aspects of the natural history of BPH center on the age-related development and course of anatomic changes in the prostate, BPH-induced dysfunctional voiding symptoms, and pathophysiologic functional changes in the bladder or upper urinary tract. The previously presented information regarding age-associated prevalence of histologic and anatomic BPH has been generated from autopsy observations and rectal or ultrasound evaluation of the prostate in clinical studies. The prevalence of histologic BPH increases progressively from the fourth (8%) through the eighth (82%) decade (27). The prevalence of gross, potentially clinically significant lesions shares this association with increasing age. For example, an autopsy study disclosed a prevalence of histologically confirmed BPH in prostates with gross enlargement of 14%, 37%, and 39%, respectively, in men 50 to 59, 60 to 69,

and older than 70 (300); this prevalence paralleled that of a palpably enlarged prostate found on rectal examination of 6,975 men evaluated for life insurance (217). Limited reported data correlating autopsy prostate weight and histology revealed prostate weights exceeding the 18-g mean normal weight by 50% or more in 61% of 69- to 70-year-olds compared with 18% of 51- to 60-year-olds (127).

The cumulative prevalence of a history and physical examination–based diagnosis of "prostatism" or BPH voiding dysfunction increased progressively from 26% to 79% from the fifth to eighth decade of life in the Baltimore longitudinal study of 1,057 men (Fig. 32.27) (140) and was recorded in 78% of the 2,049 healthy volunteers by age 80 in the Veterans Administration (VA) normative aging study (119). Prevalence as contrasted to cumulative prevalence of symptoms of prostatism was recognized in 26%, 33%, 41%, and 46% of 2,110 men ages 40 to 49, 50 to 59, 60 to 69, and over 70, respectively, in Olmsted County, Minnesota (53). Reports based on a Scottish community study yielded lower prevalence rates than the U.S. studies, and reports on a Japanese cancer screening program yielded higher prevalence rates than the U.S. studies. Interestingly, some symptoms, such as nocturia, weak stream, intermittency, urgency, and incomplete emptying, appear to increase with age, whereas others, such as frequent urination, dribbling, hesitancy, straining, and repeat urination within 10 minutes, did not. An unequivocal role for BPH in the symptom data cited should be viewed with some reservation because although symptom scores and some symptoms showed an increasing prevalence with aging, individual subjects showed a disturbing tendency to have variably present and absent symptoms (10), and several studies have documented a comparable prevalence of similar symptoms in aging women (46,127).

FIGURE 32.27. Age-specified prevalence of benign prostatic hyperplasia. *1,* Community prevalence in Bridge of Allan, Scotland, based on a case definition using symptoms, prostate size, and urinary flow rates (*n* = 699) (108a); *2,* clinical prevalence based on an enlarged prostate on manual rectal examination from a compilation of life insurance examinations (*n* = 6,975) (217); *3, 4,* clinical prevalence in the Baltimore longitudinal study of aging (BLSA) (*n* = 1,057) (140) (*3,* based on presence of an enlarged prostate on manual rectal examination; *4,* based on history and physical examination); *5,* prevalence of pathologically defined BPH from a compilation of five autopsy studies (*n* = 1,075) (27). (From Guess HM. Natural history of benign prostatic hyperplasia. In: Romas NA, Vaughn ED, eds. *Alternate methods in the treatment of benign prostatic hyperplasia.* Berlin: Springer-

Verlag, 1993, with permission.)

As indicated, the reported presence of a symptom in a given patient varies appreciably in longitudinal studies without treatment. Of men reporting hesitancy on the initial visit in the Baltimore longitudinal aging study, 27% failed to do so on the second visit and an additional 19% on the third visit (10). Barry (18), Barry and colleagues (19), and Guess (139) summarized consistency of observations from five reports of patients evaluated longitudinally for approximately 3 to 5 years with BPH voiding dysfunction. Symptomatically improved or stable individuals were noted in every study and constituted roughly one-half to two-thirds of the patients who were not operated. The prominence of this improved-stable group is probably inflated by patients with progressive symptoms electing surgery. Nevertheless, the phenomenon of apparently unexplained improved voiding based on symptom and frequently urodynamic assessment is observed repetitiously in the placebo group of short- and longer-term drug studies. Global improvement was reported in 51% and the maximum flow rate increased more than 3 mm per second in 17.7% in the placebo group of the finasteride study (121). The BPH guideline review recorded global symptomatic improvement in 40% of placebo and watchful waiting groups. Multiple factors varying from an inaccurate presumptive diagnosis to behavioral modification may play a role in this phenomenon; they must be identified and evaluated.

Prevalence data on urodynamic assessment of unselected individuals in a community setting is limited but informative. The Olmsted County survey demonstrated a progressive decrease with age of peak median urinary flow from 20 mL per second in 40- to 44-year-olds to 11.5 mL per second in 75- to 79-year-olds and an accompanying decrease of median voided volume from 355 to 222 mL. The prevalence of peak flow rates less than 15 mL per second increased from 24% to 69% in these age groups (118). Although somewhat more supportive of progressive obstruction and possible bladder decompensation, urodynamic data, including peak flow rates, voiding pressure, and residual urine, have variously been observed to become worse, become better, and remain the same (17,29). In addition, despite the age-related association of anatomic BPH and abnormal physiologic voiding parameters, the absence of a correlation in individual men between clinical and urodynamic evaluations (18,19) and limited observations of significant urodynamic evidence of detrusor instability and sensory urgency in older women clouds the interpretation of these findings (47,127).

In considering the natural history of BPH voiding dysfunction, two phenomena—acute urinary retention and development of hydronephrosis or renal failure—deserve

P.1431

special consideration because of the significant clinical impact they have. Although acute urinary retention is the indication for prostatectomy in approximately 25% to 30% of the operated patients, the risk of having acute retention was highly variable in longitudinal studies. Barry (18) and Barry and colleagues (19) projected 10-year rates from 4% to 73% (17,29). These differences probably reflect the status of the study population. In the community-based Olmsted County study (168), 57 of the 2,115 patients (1,412 were 59

years of age or younger) studied developed acute urinary retention; half of these episodes were related to surgical procedures. Only eight patients required a transurethral resection of the prostate (TURP) within 6 months of retention; one other patient had two subsequent episodes of retention. Severity of symptoms and increasing age increased risk of urinary retention, as did the presence of a low flow rate (less than 12 mL per second) or an enlarged (greater than 30 mL) prostate. The risk of acute retention was increased in young men with intermittency or the necessity to repeat void in 10 minutes. In older men, the presence of symptoms enhanced the risk of retention. The data generated suggested a 23% probability that a 60-year-old would experience acute urinary retention if he lived 20 years. In the 4-year finasteride (Pless) trial of men with BPH-recognized voiding dysfunction, untreated men had a 7% and finasteride-treated men a 3% chance of developing urinary retention. Surgery was carried out in 72% of placebo as compared with 33% of treated patients and 24% with spontaneous versus 10% with precipitated acute retention (231). These observations contrast with the infrequent (2 of 29 men) resumption of normal voiding by individuals randomly presenting in acute urinary retention with a greater than 900-mL retained urine volume observed by Taube and Gajraj (352); in their report, 15 of 34 men with less than 900 mL residual urine were able to void after catheterization without surgical intervention. Overall, approximately two-thirds of the patients presenting in acute retention failed to void. Additional data characterizing the patient population at high risk for developing acute urinary retention and their response to various treatment alternatives must be generated to guide development of reasonable management proposals for this group.

The risk of hydronephrosis with renal failure or of permanent or prolonged detrusor failure in monitored individuals is not documented. Guess (139) cites data indicating that at prostatectomy 7% of men had an elevated plasma creatinine and 5% had upper tract dilation at inpatient evaluation for prostatism. He pointed out that 17% of the cases evaluated for acute renal failure in the Boston VA Medical Center were due to urinary obstruction, with 65% of these thought to be caused by BPH. Sarmina and Resnick (317) documented previously unrecognized renal failure in 34 (3.7%) of 909 men treated for BPH from 1980 to 1986. They estimated that greater than 5% of men with unrelieved BPH bladder outlet obstruction would have chronic renal insufficiency. Patients at particular risk were those with symptoms of prostatism for more than 1 year, a history of enuresis, renal insufficiency, urinary tract infection, or urinary retention or a palpable bladder. Although they agreed with George and colleagues (110) regarding the increased risk of renal failure in men with high-pressure chronic retention, occurrence of this phenomenon has limited documentation and is unpredictable. Unquestionably, hydronephrosis and potentially, but not invariably, reversible renal failure do occur as the result of BPH (174); at one time, an appreciable cohort of the patients subjected to surgery had one or both of these complications. The discriminatory risk factors for their development remains uncertain, as does the rate at which they occur in monitored patients or in those with current sporadic medical care. The results of the prompt versus watchful waiting/delayed TURP VA study suggested compromised detrusor recovery in the watchful waiting group eventually subjected to surgery, but the role of delaying TURP in development of azotemia in two patients could not be evaluated from the information presented (95).

In the longitudinal observations summarized by Barry (18), Barry and colleagues (19), and

Guess (139), the cumulative prevalence of BPH surgery varied from 0% to 45% of the patients during limited follow-up. Surgical procedures were predominantly carried out during the first year after diagnosis in the series with high surgical rates. The risk of surgery by age 80 years was considerably greater (29%) for a man 40 years old in the VA normative aging study, carried out prospectively from 1961 to 1982 (119), than in the New Haven Hospital record study (10%), a retrospective analysis of 1953 to 1961 data (218). In both, the incidence rates for BPH surgery increased through the eighth decade. In the Baltimore longitudinal study of aging (10), a change in size and force of the urinary stream and a sensation of incomplete emptying of the bladder in a patient with digitally detected prostatic enlargement were predictive of future prostatectomy. In the Kaiser Permante medical care program analysis cited by Guess (139), the symptoms predictive of prostatectomy were hesitancy, a weak stream, painful urination, loss of bladder control, and nocturia.

Two other observations are of interest. Despite the lack of correlation between prostate size and outflow obstruction, a correlation seems to exist between election of surgical intervention and prostate size (27). Second, there is suggestive evidence from postmortem anatomic assessments supporting clinical impressions that the prostate of some aging men may undergo regression in size (350).

Indications for Treatment

The following are accepted criteria for interventional relief of bladder neck obstruction caused by BPH.

Acute urinary retention is often indicative of end-stage bladder decompensation requiring operative relief. The patient whose retention is triggered by ingestion of drugs such

as α-adrenergic agonists or anticholinergic agents may void satisfactorily once the medication is stopped and the bladder drained for a time. A supervised attempt at decatheterization for minimally symptomatic patients with an incident-related (e.g., postoperative or acute bacterial prostatitis) or spontaneous episode of retention is often reasonable. Use of α-adrenergic antagonists in conjunction with this voiding trial is worthwhile . For repeated episodes of retention, management by intermittent catheterization or continued catheter drainage is possible but is usually an unacceptable alternative to an operative approach. The patient with urinary retention is usually treated satisfactorily by insertion of a urethral catheter. For difficult catheterizations, a percutaneous suprapubic cystotomy tube remains an appropriate alternative that is usually well tolerated and associated with few catheter-related complications. If chronic retention is suspected, the bladder should be emptied gradually to avoid diffuse mucosal cracking and bleeding that may follow rapid decompression. Use of a variety of internalized catheters is currently being evaluated in selected patients at high risk.

Bilateral hydronephrosis with renal functional impairment requires relief of the obstruction to preserve the integrity of the upper tracts. On catheter insertion, a postobstructive diuresis may ensue, requiring meticulous fluid and electrolyte management. The patient's general condition should be optimized before operative intervention is undertaken.

The presence of multiple bladder stones, prominent narrow-necked bladder diverticula, overflow incontinence, and other signs of end-stage bladder decompensation are indications for therapeutic intervention. Recurrent or chronic urinary tract infections caused by an elevated residual urine are also an indication for considering intervention. Acute or chronic bacterial prostatitis should be excluded as a possible source of infection. A careful history, physical examination, and lower tract localization cultures should help clarify this issue.

Gross hematuria is an infrequent but legitimate indication for so-called prostatectomy, particularly when the episodes are multiple and associated with clot retention or significant blood loss. The usual limited initial hematuria associated with BPH is commonly best managed conservatively. Antiandrogen measures such as the use of finasteride almost always have a favorable impact on recurrent prostatic bleeding (96).

Obstructive and irritative symptoms that significantly interfere with the quality of life of the patient are common indications to consider prostatic surgery and other therapeutic approaches. The cause of the symptoms should be established with a very high degree of probability. In the past, most patients have had multiple indications to support the decision to initiate therapy (239). Both the urologic surgeon and the patient must be clearly aware of the results that can be expected and the risks involved in achieving them.