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Peyronie's Disease: Etiology, Medical, and Surgical Therapy

Review

WAYNE J. G. HELLSTROM AND TRINITY J. BIVALACQUA

From the Department of Urology, Tulane University School of Medicine, New Orleans, Louisiana.

Since the first clinical series on penile curvature was reported in 1743 by Francois Gigot de la Peyronie, the etiology and mechanism of this well-recognized symptom complex has remained undetermined. Peyronie's disease is a localized connective tissue disorder characterized by changes in the collagen composition of the tunica albuginea of the penis. The end result is a fibrous plaque that contains an excessive amount of collagen, alterations in the elastin framework, and fibroblastic proliferation that consequently alters penile anatomy and may dramatically affect erectile function. The tunica albuginea plays a vital role in erection because of its essential properties of penile elasticity, rigidity, compliance, and veno-occlusion (Aboseif and Lue, 1988). Erectile dysfunction is known to occur in at least 20% of men with Peyronie's disease and is recognized to affect quality of life, with 77% of Peyronie's men demonstrating significant psychological effects (Gelbard et al, 1990; Carson, 1999).

Peyronie's disease usually affects males between the ages of 40 and 70, with a reported 0.39 to 3% incidence; however, there are numerous reports of cases in younger individuals (Carson, 1981; Gelbard et al, 1990; Lindsay et al, 1991). The actual prevalence of this disease may be higher due to patient embarrassment and limited reporting of this disorder by physicians. Along these lines, most clinicians note that the number of Peyronie's patients has increased since the advent of oral sildenafil (Viagra, Pfizer). With more men being successfully treated for erectile dysfunction (ED), an increasing number of Peyronie's cases are becoming manifest and presenting for evaluation. Men with Peyronie's disease may complain of penile pain, penile angulation, palpable plaque, and decreased erectile function. The rigid plaque that is the cause of the aforementioned symptoms is found on the side of the corpus cavernosum to which the curvature is directed. The characteristic Peyronie's plaque is most commonly located on the dorsal aspect of the penis, causing an upward curvature during erection (Figure A). However, plaques may be identified on the ventral aspect or on the lateral side of the penis causing a downward curvature (Figure B). Several proposed theories as to the origin of Peyronie's disease include: vitamin E deficiency; the use of beta-blocking agents; increased levels of serotonin, as in carcinoid syndrome; genetic disorders; and repetitive vascular trauma inciting a low-level autoimmune response with fibrosis and plaque formation (Scardino and Scott, 1949; Yudkin, 1977; Van de Berg et al, 1982; Somers et al, 1987; Jarow and Lowe, 1997). A number of systemic fibrosing conditions are known to occur concomitantly with Peyronie's disease (Ordi et al, 1990). Peyronie's patients may have a genetic predisposition, as witnessed by its association with Dupuytren's contracture and HLA-B7 antigens (Chilton et al, 1982; Nyberg et al, 1982). More current proposals suggest that fibrosis and collagen changes of the tunica albuginea are the result of an inflammatory process triggered by vascular trauma (Jarow and Lowe, 1997; Carson, 1999). Following trauma or injury to the penis, the release of cytokines activate fibroblast proliferation, and collagen, the main extracellular matrix component of a Peyronie's plaque, is produced. Therefore, Peyronie's disease has been defined as a wound-healing disorder, much like the dermatologic conditions of keloid formation, hypertrophic scarring, and Dupuytren's contracture (Levine et al, 1994). Despite many etiological theories and the myriad of medical and surgical treatments proposed for men with Peyronie's disease, there has been a limited number of advances and scientific understanding about its pathophysiology.

Pathophysiology

Peyronie's disease affects primarily the tunica albuginea of the penis. Elastic fibers located within the tunica albuginea of the penis form an irregular latticed framework upon which collagen rests. These elastic fibers are important in maintaining the structure of the collagen bundles. These 2 structural components are essential to penile erection because they permit both an increase in girth and length during tumescence (Aboseif and Lue, 1988; Hsu et al, 1994). Any defect of the tunical collagen or elastic fiber network may lead to significant alterations in the hemodynamics of erection. ED is a major quality-of-life

Correspondence to: Dr. Wayne J. G. Hellstrom, Section of Andrology and Male Sexual Dysfunction, Department of Urology, Tulane University School of Medicine, New Orleans, LA 70112 (e-mail: whellst@tmcpop.tmc.tulane.edu).

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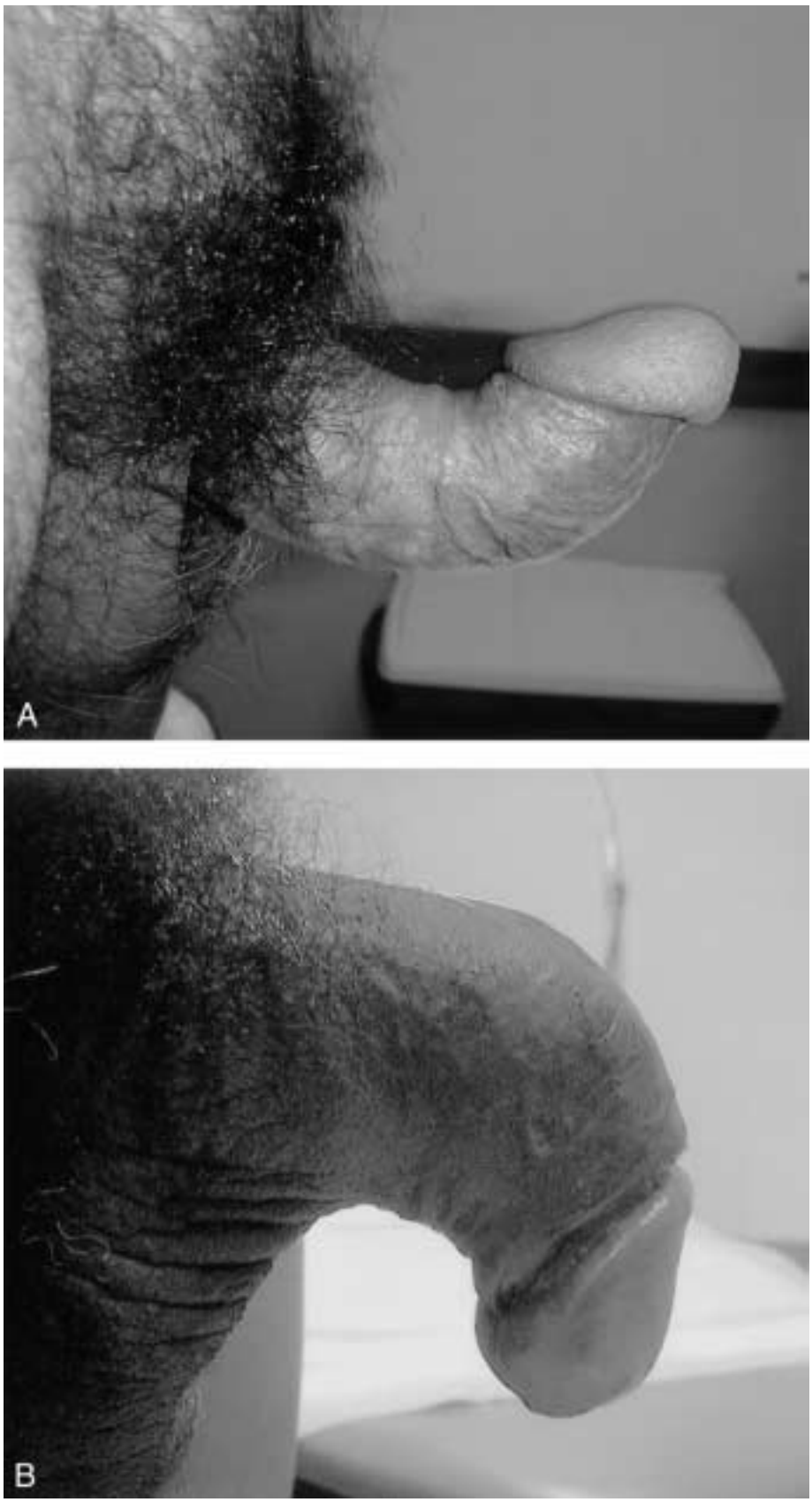

Figure **(A)** Erect penis demonstrating dorsal curvature. **(B)** Erect penis demonstrating ventral curvature in men suffering from Peyronie's disease.

issue, with estimates of 20 to 30 million men suffering from this condition in the United States alone (NIH Consensus Conference, 1993; Feldman et al, 1994). At least 20% of patients with Peyronie's disease suffer with ED (Gelbard et al, 1990; Carson, 1999).

The histopathology of Peyronie's disease reveals an inflammatory process, characterized by chronic lymphocytic and plasmacytic infiltration of the tunica albuginea and the surrounding erectile tissues. The origin of the initial inflammatory process that leads to fibrosis, calcification, and plaque formation in the tunica albuginea is unknown. Devine et al have postulated that minor penile trauma can occur during sexual intercourse, whereby the corpora cavernosa bend and stretch, resulting in a delamination injury of the tunica albuginea predominantly at the dorsal, midline septum (Devine et al, 1991). This process incites further inflammation, induration, and fibrin deposition between the layers of the tunica albuginea, thereby activating the proliferation of local fibroblasts and leukocytes. Levine and colleagues have postulated that following injury to the penis, a process of wound healing occurs, with fibroblast proliferation and extracellular matrix deposition (Levine et al, 1994). It is postulated that at this juncture of the wound-healing process the balance between extracellular matrix and scar tissue formation exceeds that of degradation of both collagen and extracellular matrix because of abnormal fibroblast activity. Fibrin residues stimulate an amplification of histocytes and increased collagen deposition that infiltrate the tunica albuginea.

There have been reports of changes in the collagen content of the tunica albuginea of patients with Peyronie's disease (Somers et al, 1989; Luangkhot et al, 1992). Type I and III collagen expression is commonly present in penile scar tissue, while type III collagen is found more abundantly in Peyronie's plaques. Moreover, the demonstration of increased type III collagen in the normal penile tissue adjacent to the plaque tissue suggests that this disease is not specific to the plaque but may be more generalized throughout the corporal tissues (Mersdorf et al, 1991; Chiang et al, 1992; Luangkhot et al, 1992; Iacono et al, 1993). Of particular interest is the observation of increased type III collagen expression in patients with venogenic impotence (Chiang et al, 1992). In men who suffer from veno-occulsive dysfunction or who have Peyronie's disease, type III collagen fibers are found abundantly in the tunica, while this finding is rare in the tunica albuginea of potent men.

Elastic fiber concentrations in the tunica are also significantly decreased in Peyronie's patients and are significantly lower in impotent men with Peyronie's compared to Peyronie's patients who maintain potency. Antibodies to elastin are present in all individuals; however, Peyronie's patients exhibit increased levels of antitropoelastin (reflecting elastin synthesis) and anti-α-elastin (reflecting elastin destruction) (Stewart et al, 1994), giving reason to believe that an autoimmune mechanism specifically affecting the elastin framework may be involved in the pathogenesis of Peyronie's disease.

Collagen synthesis in adult tissues is subject to regulation by a variety of endogenous and exogenous factors. Biologically active peptides, such as interleukin-1, tumor necrosis factor, epidermal growth factor, and transforming growth factor beta (TGF-β), have been implicated in normal collagen synthesis and fibrosis (Border and Noble, 1994; Nikolic-Paterson et al, 1996; Zhang and Phan, 1996). Among them, TGF-β has been shown to be involved in many chronic fibrotic conditions, in addition to being involved in numerous vital processes, such as inflammation, stimulation of extracellular matrix, and the normal healing process (Border and Noble, 1994). TGF-β is a cytokine that is vital to tissue repair; however, an excess may induce tissue damage and scarring as witnessed in a variety of connective tissue diseases, eg, pulmonary fibrosis, fibrotic liver disease, and systemic sclerosis (Border and Noble, 1994). Furthermore, TGF-β1 is the isoform most implicated in tissue fibrosis and is up-regulated in response to tissue injury. Recently, El-Sakka and colleagues have demonstrated an up-regulation of TGF-β in the tunica albuginea of Peyronie's disease patients when compared to the tunical tissue of men without Peyronie's disease (El-Sakka et al, 1997b). The expression of TGF-β mRNA and protein in the tunica albuginea of the male penis as well as the induction of collagen synthesis in cell culture suggests a role for TGF-β in corpus cavernosum tissue synthesis (Moreland et al, 1995; El-Sakka et al, 1997b).

A new animal model for Peyronie's disease has been proposed by El-Sakka and colleagues (El-Sakka et al, 1997a, 1998). These authors have explored the role of TGF-β and surgical trauma in the induction of a Peyronie's-like condition in the rat. Their studies demonstrate histological and ultrastructural alterations in the rat penis after a Peyronie's state was induced. Histological changes observed in this animal model included chronic inflammatory infiltration; focal and diffuse elastosis; and thickening, disorganization, and clumping of the tunica albuginea (El-Sakka et al, 1997a, 1998). The ultrastructural changes to the penis included dense collagen bundles and separation of neuronal fibers by clumps of packed collagen. Bivalacqua and colleagues further characterized this rat model of Peyronie's disease by demonstrating a role for nuclear factor kappa B (NF-κB), a transcription factor that regulates the expression of several genes that encode adhesion molecules (Bivalacqua et al, 1999). These authors demonstrated the immunohistochemical presence of NF-κB in the initiation of a Peyronie's-like condition in the rat during the first 3 weeks after TGF-β injection and injury to the rat penis (Bivalacqua et al, 1999). These rat

penis studies demonstrate that TGF-β injection and surgical injury can induce symptoms similar to those found in humans with Peyronie's disease and that this animal model has the potential for further investigations into the mechanisms of Peyronie's disease.

Medical Therapy

A definitive medical therapy for Peyronie's disease has still not been established. Patients often complain of penile curvature, penile nodules, penile pain during erection, and/or ED. Peyronie's disease can be simplistically classified into 2 phases: 1) an acute inflammatory phase that persists for approximately 6 to 18 months, in which patients present with pain, slight penile curvature, and nodule formation; and 2) a chronic phase in which patients present with stable plaque size, penile curvature, and in some instances, complete ED. At least 20% of Peyronie's patients have ED, and 18% have veno-occlusive dysfunction (Gelbard et al, 1990; Amin et al, 1993; Carson, 1999). In 1990, Gelbard and colleagues reported that approximately 13% of patients with Peyronie's disease had complete resolution of their plaques with time (Gelbard et al, 1990). Most authorities suggest that patients be informed that their symptoms will most likely not resolve spontaneously, hence medical therapy should be implemented. Numerous studies have shown that the Peyronie's patients most likely to benefit from medical therapy for their symptoms are those patients with early-stage disease (Devine et al, 1991).

Some of the more common medical treatment options for patients with Peyronie's disease include oral therapy with vitamin E, potassium aminobenzoate (Potaba), tamoxifen, or colchicine; and intralesional injection therapy with collagenase, steroids, calcium channel blockers, or interferon-α2b (Scardino and Scott, 1949; Hasche-Klunder, 1978; Ralph et al, 1992; Gelbard et al, 1993; Akkus et al, 1994; Levine et al, 1994; Ahuja et al, 1999a). Because there is no documented progression of Peyronie's disease to malignancy, patients with mild curvature, relatively little penile pain, or minimal ED in most instances require no further therapy and can be followed conservatively.

Vitamin E therapy remains a popular treatment modality in part because of its mild side effects and low cost. The first report on this antioxidant was in 1948 by Scardino and Scott, in which they observed a 78% decrease in penile curvature and a 91% reduction in plaque size in an uncontrolled study (Scardino and Scott, 1949). Unfortunately, most published studies on the various medical treatments for Peyronie's disease are flawed in that they do not include proper control groups, have limited objective evaluation, and have short-term follow-ups. At the NIH Conference on Peyronie's Disease in 1993, Devine and Snow presented a study in which 105 patients receiving oral vitamin E subjectively reported a 99% reduction in pain and a 13% reduction in penile curvature, despite the fact that 70% of the patients had no objective change in their condition.

The use of oral potassium aminobenzoate (Potaba) in the treatment of Peyronie's disease was first reported in 1959 (Zarafonetis and Horrax, 1959). In this study of 21 Peyronie's patients, 100% had a reduction in pain, 82% had improved penile curvature, and 76% had resolution of plaque size (Zarafonetis and Horrax, 1959). The exact mechanism of action of this drug is uncertain but may be due to an increase in monoamine oxidase, decreased serotonin, and/or an increased utilization of oxygen by tissues. Recently, Carson reported that in 32 Peyronie's patients receiving 12 g of Potaba daily for 3 months complete resolution of penile angulation occurred in 8 of 31 patients, with 18 of 31 patients demonstrating decreased plaque size (Carson, 1997). Unfortunately, the expense and high incidence of gastrointestinal upset with this medication often leads to low compliance (Carson, 1997).

Tamoxifen is a nonsteroidal antiestrogen that has been shown to have a beneficial effect in the treatment of desmoid tumors, a condition with histologic properties similar to Peyronie's disease. The authors report that tamoxifen facilitates the release of TGF-β from human fibroblasts in vitro, suggesting that it can inhibit the inflammatory response and decrease fibroblast production and/or angiogenesis (Colletta et al, 1990). As noted, TGF-β in small amounts regulates inflammation, the immune response, and tissue repair by deactivating macrophages and T lymphocytes. However, if large amounts of this growth factor are produced, it can augment tissue fibrosis (Border and Noble, 1994). In a study with 36 patients receiving 20 mg of tamoxifen twice daily for 3 months, Ralph et al. reported that 16 of 20 patients had improvement in penile pain, 11 of 31 patients had improvement in penile curvature, and 12 of 35 patients had a reduction in plaque size (Ralph et al, 1992). However, because of the lack of long-term studies, limited knowledge on its mechanism of action, and a small amount of data on its side effect profile, oral tamoxifen for the treatment of Peyronie's disease has not become commonplace in American practice.

Colchicine is an agent with anti-inflammatory activity that can decrease collagen synthesis and stimulate collagenase activity (Harris and Krane, 1971). Colchicine interferes with the transcellular movement of collagen and diminishes the activity of the enzymes responsible for collagen processing (Harris and Krane, 1971; Fell et al, 1989). Akkus and colleagues reported on 24 patients treated with colchicine in a noncontrolled study for 3 to 5 months, with 11% reporting a slight decrease in cur-

vature, 26% reporting a marked decrease in curvature, and 50% observing a decrease in plaque size (Akkus et al, 1994). However, erectile status and hour-glass deformity did not improve in any of the patients. Levine has stated that in over 30 patients using colchicines, most had poor tolerance, with about 50% of patients reporting GI upset (Levine, 1998). Other oral agents reported in the literature (eg, procarbazine, steroids) may have some therapeutic efficacy in treating Peyronie's disease.

Intralesional injection of various agents has been proposed as a less invasive option than surgery for debilitating Peyronie's disease. An early report with the steroid dexamethasone demonstrated a reduction in plaque size and penile pain (Winter and Khanna, 1954). In 1980, Williams and Green conducted a study in which 45 patients received intralesional injections of triamcinolone hexacetonide, a long-acting glucocorticoid, at 6 weekly intervals for 36 weeks. They reported that 36% of the patients had complete or marked improvement in their symptoms; patients receiving the most benefit from therapy were those with small, firm, discrete plaques (Williams and Green, 1980). However, intralesional therapy with steroids may cause severe local side effects, such as local tissue atrophy, and may complicate subsequent surgery because of fibrosis (Winter and Khanna, 1954; Williams and Green, 1980).

Several in vitro studies have demonstrated the efficacy of various anti-inflammatory agents and calcium channel blockers in modifying the expression of cytokines and increasing collegenase activity (Gelbard et al, 1982; Kelly, 1985). In 1982, Gelbard and colleagues revealed that purified clostridial collagenase in vitro could dissolve surgically excised Peyronie's plaques (Gelbard et al, 1982). The foundations of modern intralesional therapy can be attributed to these early studies by Gelbard et al. These authors injected purified collagenase into Peyronie's plaques as described in their earlier in vitro studies, with 65% of 31 patients showing improvement in curvature (Gelbard et al, 1985). In a more recent report, they demonstrated a significant benefit of intralesional collegenase over placebo in patients with minimal Peyronie's disease; however, patients with more severe Peyronie's disease showed little clinical benefit after intralesional collagenase (Gelbard et al, 1993).

The use of intralesional verapamil, a calcium channel blocker, for the treatment of Peyronie's disease has gained attention in the past 5 years since Levine published his report in 1994 (Levine et al, 1994). His clinical approach was based on earlier in vitro studies in fibroblasts demonstrating the dependence of extracellular transport of collagen on the presence of calcium and the increased collagenase activity induced by verapamil (Lee and Ping, 1990). In Levine's first study, which was uncontrolled, intralesional injection of verapamil in a dose of 10 mg reduced pain in 91% of patients; hour-glass deformity subjectively improved in 100%, objective measures of curvature improved in 42%, and sexual function improved in 58% (Levine et al, 1994). Recently, Rehman et al demonstrated the therapeutic benefit of intralesional verapamil in a single-blind study and concluded that it was a reasonable approach in patients with noncalcified plaques and penile angulation of less than 30° (Rehman et al, 1998). Complications in these studies were minimal, with no infection, hypotension, or arrhythmias being reported.

The interferons are a group of naturally occurring, low molecular weight proteins and glycoproteins that play an integral role in the immune system by interfering with viruses and causing antiproliferative and antitumorigenic effects (Stuart-Harris et al, 1992). The potential use of intralesional interferons was demonstrated in 1991 by Duncan and colleagues, who reported on the in vitro effects of interferons α-2b and -γ on the production of collagen in Peyronie's disease-derived human fibroblasts (Duncan et al, 1991). They documented that the interferons inhibited fibroblast proliferation, which diminished collagen production, and additionally that interferon-α2b stimulated collagenase activity. Ahuja et al, using an in vitro model of corpora cavernosal-derived myofibroblasts, demonstrated stimulation of collagen production with exposure to oxygen-free radicals and diminished collagen production in the presence of interferon-α (Ahuja et al, 1999b). Furthermore, interferon α-2b is recognized to decrease effectively keloid scars and scleroderma (Berman and Duncan, 1989). Based on the success of intralesional collagenase and verapamil and the recognized in vitro effects of interferon-α, the first report with intralesional interferon-α2b demonstrated decreased penile pain, penile curvature, and plaque size (Wegner et al, 1995). In 1997, further support for this modality was provided by Judge and Wisniewski in 13 patients suffering from Peyronie's disease; 3 men received intralesional saline as a control, while the remaining 10 underwent injection with 1.5×10^6 units of interferon-α2b 3 times per week for 3 weeks. There were no changes noted in the control subjects, but all study drug patients reported resolution of pain, decreased penile curvature, plaque softening, and decreased plaque size (Judge and Wisniewski, 1997). Ahuja et al recently demonstrated that interferon α-2b was efficacious as an intralesional therapy for Peyronie's disease. They reported that 9 of 10 patients (90%) initially reporting penile pain on erection had resolution of their phallagia, 65% had significant improvement in curvature ranging from 20 to 90%, and 85% demonstrated an objective decrease in plaque size (Ahuja et al, 1999a). Complications included sinusitis, flu-like symptoms, and arthralgias. Future multicenter protocols employing intralesional interferon therapy for Peyronie's disease are warranted and

must employ some form of placebo-control crossover design in order for definitive conclusions to be made regarding the efficacy of this therapy.

Shock-wave therapy for the reduction of Peyronie's symptoms has been proposed by a number of European investigators as a relatively noninvasive treatment. Recently, Gianneo et al reported a study of 153 patients who received 6 to 8 lithotripsy treatments with a 7.5-Mhz inline ultrasound scanner. Their results reported that shock-wave therapy decreased penile pain and improved the elasticity of the plaque region but did not significantly affect penile curvature (Gianneo et al, 1999). Most authorities suggest that this therapy will induce more inflammation and traumatic scarring to the tunica albuginea and hence do not recommend its use in the treatment of Peyronie's disease. The use of iontophoresis, the electrokinetic transport of charged molecules, for the enhancement of transdermal drug transport has been shown to benefit soft tissue diseases (Wang and Griffith, 1993). Montorsi et al demonstrated in a placebo-controlled study that iontophoretic delivery of dexamethasone and verapamil could be efficacious in the treatment of Peyronie's disease (Montorsi et al, 1995). However, both shock-wave therapy and iontophoresis are difficult to recommend due to the absence of long-term results and side-effect profiles.

A better understanding of the inflammatory response and the mechanisms by which fibrosis occurs in the tunica albuginea will no doubt offer new avenues for future medical intervention of Peyronie's disease. Agents that modify cytokine action, fibroblast function, and extracellular matrix deposition head the list in this area of investigation.

Surgical Therapy

Peyronie's disease has a variety of clinical presentations and likewise may respond to medical therapies differently. After counseling Peyronie's patients about the lack of malignant progression, the astute clinician recognizes the limitations of any noninvasive therapy for severe disabling disease. In those instances, where disease precludes sexual intercourse and progression has stabilized (usually by 12 months), surgery may be the only alternative.

Patients with inadequate penile rigidity who prefer to not have penile prosthesis implantation should then undergo diagnostic studies. In most institutions, penile duplex Doppler ultrasonography combined with intracorporal injection of a vasoactive agent and visual sexual stimulation provides an excellent assessment of the penile deformity and the vascular status of the penis. If the patient has significant vascular insufficiency, prosthesis implantation is recommended. However, as a caveat, with the future of multiagent and gene therapies, this guideline may not be as certain in the years to come.

Because of the variations in penile anatomy and different clinical presentations of Peyronie's disease, no single operation can be applied in all cases. In a man with a longer penis and more distal curvature, a Nesbit or plication procedure is usually indicated (Coughlin et al, 1984; Mufti et al, 1991; Poulsen and Kirkeby, 1995). These procedures are simple to perform, involve limited patient morbidity (such as sensory nerve deficits or glans softening), and give the patients excellent cosmetic results. Minimal shortening of the erect penis is a recognized side effect of this intervention. These techniques typically utilize a subcoronal incision, creation of an intraoperative artificial erection, and the use of nonabsorbable sutures with hidden knots. Patients are discharged home on the same day, and after a 6- to 8-week period of convalescence, the vast majority report satisfactory functional results.

If a man has a shorter penis and/or a proximal Peyronie's plaque, then excision and grafting may be more in order. Grafting materials may be autogenous (such as dermis, saphenous vein, tunica vaginalis, temporalis fascia, vascularized preputial, and processed cadaveric pericardium) or synthetic (such as Dacron, Gore-Tex, and silastic) (Devine and Horton, 1974; Treiber and Gilbert, 1991; Fournier et al, 1993; Ganabathi et al, 1995; Krishnamurti, 1995; Yachia et al, 1995; Hellstrom and Reddy, 2000). In most instances, the graft material chosen is based on a combination of journal reports, physician historical success, availability, and physician comfort. After degloving the penis, either the neurovascular bundles are dissected and elevated for dorsal plaques or the corpora spongiosum freed for ventral plaques. After incision or excision of the diseased area, the graft material is sewn into place before closure and placement of a light compression dressing.

When vascular compromise mandates placement of a malleable or inflatable penile prosthesis, this alone may correct the penile abnormality (Carson et al, 1983). This is especially likely if the man has a relatively thin tunica albuginea and significant fibrosis has not occurred. In cases where the penile prosthesis implantation alone does not straighten the penis, an attempt at manual modeling is recommended (Wilson and Delk, 1994). This technique involves forcible manual manipulation of the penis over an inflated prosthesis. In most instances, significant straightening is accomplished. There are recognized complications from this technique, including urethral perforation and infection (which are known to occur in any prosthesis operation; Wilson and Delk, 1994).

In situations where modeling is ineffective or the penile defect is very severe, eg, bottlenecking, unilateral cavi-

tation, or curvatures greater than 90°, use of grafting materials in addition to prosthesis implantation is warranted. Fortunately, most patients respond extremely well to these surgical reconstructions and are among the most grateful urologic patients.

Summary

Peyronie's disease remains an enigma. With the recent introduction of an animal model for Peyronie's disease, the entry of a number of double-blind placebo-controlled clinical trials, and the application of new molecular diagnostic methods, the investigation of this wound-healing disorder of the penile tunica albuginea should illuminate many of the unknowns. Investigators need to be open to innovations in other fields of medicine involving idiopathic fibrosing conditions in other organ systems, eg, Dupuytren's contracture, keloids, hypertrophic scarring, etc. Applications from these other disciplines will undoubtedly widen our scope about Peyronie's disease.

While a minority of patients respond with observation alone, most authorities recommend at least a trial of medical therapy with a safe, inexpensive, and well-tolerated agent, as early-stage disease is reputedly more likely to respond better than patients with established, longstanding Peyronie's plaques.

The reintroduction of intralesional therapies (verapamil and interferon α-2b) provides the clinician with an alternative minimally invasive intervention that has promising possibilities. In severe fibrotic or calcified plaques or with major structural abnormalities, the judicious use of surgery with or without grafting materials and a penile prosthesis can restore many men back to their previous level of high esteem and provide both partners an excellent quality of life.

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