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Models of Inflammation of the Lower Urinary Tract

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Abstract

Inflammation of the lower urinary tract occurs frequently in people. The causes remain obscure, with the exception of urinary tract infection. Animal models have proven useful for investigating and assessing mechanisms underlying symptoms associated with lower urinary tract inflammation and options for suppressing these symptoms. This review will discuss various animal models of lower urinary tract inflammation, including feline spontaneous (interstitial) cystitis, neurogenic cystitis, autoimmune cystitis, cystitis induced by intravesical instillation of chemicals or bacterial products (particularly lipopolysaccharide or LPS), and prostatic inflammation initiated by transurethral instillation of bacteria. Animal models will continue to be of significant value in identifying mechanisms resulting in bladder inflammation, but the relevance of some of these models to the causes underlying clinical disease is unclear. This is primarily because of the lack of understanding of causes of these disorders in people. Comparative and translational studies are required if the full potential of findings obtained with animal models to improve prevention and treatment of lower urinary tract inflammation in people is to be realized.

Inflammation of the lower urinary tract is relatively common and is most often the result of urinary tract infection. Urinary tract infection is the second most common infectious disorder of humans and results in 8.3 million doctor visits annually (1). All but about 5% of these patients exhibit symptoms of inflammation, including pain, urgency, and increased frequency (2). Painful Bladder Syndrome/Interstitial Cystitis (PBS/IC) is a poorly characterized syndrome of unknown cause(s) characterized by pain, increased urgency, and increased frequency. A recent review of this disorder found studies estimating a prevalence ranging from less than 1% to 11% of all women above the age of 19 (3), and it is thought that PBS/IC affects more than one million patients in the US alone (4). The diagnosis of PBS/IC is typically made by exclusion of other causes of symptoms (including infection), and inflammation of the bladder is confirmed by biopsy in many patients diagnosed with PBS/IC (5,6). Pain characteristically accompanies inflammation of the lower urinary tract. Inflammation is also commonly identified in prostate biopsy samples obtained from patients with benign prostatic hyperplasia (BPH) (7-9). Although pain is not consistently correlated with the presence of BPH, a subset of these patients complains of pain associated with the lower urinary tract (10,11). While a variety of neoplastic or parasitic disorders may occasionally cause inflammation of the lower urinary tract, these disorders occur far less frequently.

Clearly, it would be unethical and immoral to perform mechanistic studies using human subjects, but investigators should keep in mind the influence genetics and environment may have on results. Animal models (that typically use inbred stains of rodents) of clinical disorders resulting in lower urinary tract inflammation suffer from many of the same

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limitations associated with clinical research focused on human (outbred) subjects. Bacterial cystitis can be induced in rodents, but the response to infection varies widely dependent on the strain of the host and the particular bacteria used to induce infection (12,13). When using animal models to investigate mechanisms resulting in lower urinary tract inflammation, one must be aware of the impact of genetic differences among strains and species on results obtained. Although it is perfectly reasonable to assume that the biological response of the lower urinary tract of animals to a particular infectious or irritating stimulus is consistent and reproducible and accurately reflects the physiology of that species, genetic differences within and between species may render the direct relevance of the findings to specific human patients suspect. The use of animal models to investigate lower urinary tract inflammation is also complicated by the nearly complete lack of understanding of the underlying causes and pathogenesis of PBS/IC. In the absence of a clear understanding of the factors resulting in the onset of this disorder, it is difficult to state with absolute certainty that results of studies using animal models recapitulate events resulting in PBS/IC.

Thus, results of experiments using animal models of lower urinary tract inflammation should be viewed as having greatest relevance to mechanisms of pathophysiology leading to inflammation of the lower urinary tract. This does not mean that animal models of lower urinary tract inflammation are without value. Results of experiments performed with animal models of lower urinary tract inflammation have clearly provided the basis for development of therapies that relieve symptoms in some patients. Some examples of this include intravesical instillation of resiniferatoxin or botulinin toxin A and development of various antimicrobial agents. Resiniferatoxin is a potent analogue of capsaicin that desensitizes the transient receptor potential vanilloid type 1 (TRPV1), a cation channel that is thought to play a key role in transmitting nociceptive sensation from the bladder (14,15). Intravesical resiniferatoxin decreases spinal c-fos expression and increases bladder filling volume prior to stimulation of reflex micturition in rats with chronic inflamed urinary bladders (16). Injection of botulinum toxin type A into the bladder walls of rats (17) or intravesical instillation of this compound into the bladders of rats (18) helped to normalize bladder function in the presence of chemical cystitis or partial outflow obstruction, respectively. However, the fact that not all patients consistently respond to these treatments simply reinforces the complexity of the pathogenesis of inflammation of the lower urinary tract.

The purpose of this review is to describe animal models of lower urinary tract inflammation and to discuss the positive aspects and limitations of these models. Table 1 lists animal models of lower urinary tract inflammation and the references cited for each in this review.Models that will be discussed include feline spontaneous (interstitial) cystitis, neurogenic cystitis, autoimmune cystitis, and cystitis induced by intravesical instillation of chemicals or bacterial products (particularly lipopolysaccharide or LPS). A recently-described model of prostatic inflammation initiated by transurethral instillation of bacteria will also be described.

Feline Spontaneous (Interstitial) Cystitis

It has long been recognized that some domestic cats develop bladder disease that is characterized by increased urinary frequency, urgency, and hematuria (19). Early studies suggested that this disorder may be due to infection of the bladder by calicivirus or herpesvirus (20-22). However, despite the ability of these investigators to experimentally replicate the disorder by intravesical viral instillation, other investigators have been unable to duplicate these findings, and most authorities do not believe that there is an underlying viral cause of this syndrome in cats (reviewed in 23). Similarly, although bacteria have been identified in the urine from some of these cats, careful study demonstrated that bacteria

could be cultured from the urine in a very small percentage (possibly less than 1%) of these cats (24-26).

In 1993, Buffington et al. reported that, similar to patients with IC/PBS, these cats excrete less glycosaminoglycan in the urine and further suggested that this disorder in cats was analogous to IC/PBS in humans (27). Subsequent studies using cats with this disorder demonstrated numerous similarities to patients with IC/PBS, including increased permeability of the bladder wall (28). There is significant interest in communication between the urothelium (epithelial cells lining the bladder) and afferent innervation of the bladder, and it has been demonstrated that urothelial cells express receptors for many neurotransmitters, as well as having the capacity to produce compounds that mediate pain and inflammation (reviewed in 29). Substance P is a neurotransmitter that plays a key role in transmission of painful sensations (30), and nerve growth factor is a neurotrophin that also stimulates nociception in peripheral tissues (31). It has been reported that urothelial cells from the bladders of cats with spontaneous (or interstitial) cystitis express increased amounts of substance P and nerve growth factor (32), as has been observed in bladder biopsies from humans with IC/PBS (33,34). Similarly, alterations in the profile of expression of purinergic receptors and release of ATP by urothelial cells has been described in both cats with spontaneous cystitis (35,26) and humans with IC/PBS (37,38). Both of these substances have the capacity to stimulate nociceptive input and contribute to inflammation. A more comprehensive analysis of similarities between feline spontaneous (interstitial) cystitis and IC/PBS in humans has been published (39).

Feline spontaneous (interstitial) cystitis has the distinct advantage of occurring in the absence of administration of exogenous substances that injure the bladder. While many similarities between cats with this disorder and humans with IC/PBS have been identified, it is still unclear whether or not this disorder in cats is analogous to IC/PBS in humans, if for no other reason than the fact that the underlying causes of, and mechanisms resulting in, IC/PBS are have not been definitively identified. Thus, as with many other animal models of human disease, studying cats with spontaneous cystitis of unknown cause(s) can provide clues to the processes that result in, or cause sequela to, IC/PBS in humans, but it remains difficult to accept the concept that this model replicates all aspects of IC/PBS in humans.

Neurogenic Cystitis

Neurogenic Cystitis

Neurogenic inflammation has classically been considered the result of antidromic stimulation of afferent sensory nerves (thought to be primarily unmyelinated C fibers or lightly myelinated Aδ fibers in the bladder) resulting in release of neurotransmitters that cause pain and inflammation (40,41). This phenomenon has been reported to affect several organs, including the bladder, skin, gut, lungs, airways, eyes, and joints (42-45). Neuropeptides that mediate neurogenic inflammation include substance P, neurokinin A, and calcitonin gene-related peptide (CGRP), and these substances are released by nerve fibers that express transient receptor vanilloid 1 (TRPV1) channel (46). Interestingly, it has also been reported that neurons expressing both α_1-adrenoceptors and TRPV1 are present in lumbar and sacral dorsal root ganglia and that exposure of these neurons to phenylephrine stimulated release of substance P, providing strong evidence that the bladder also receives afferent innervation from the sympathetic nervous system (47). Other investigators have reported that sympathetic nerves have the capacity to synthesize and release substance P, neurokinin A, and CGRP, and it is widely accepted that the sympathetic nervous system participates in neurogenic inflammation (48-50).

The TRPV1 channel is activated by capsaicin or resiniferatoxin, resulting in death or desensitization of the afferent fiber, and desensitization of afferent fibers is thought to be the mechanism underlying pain relief provided by intravesicular instillation of these compounds in patients with IC/PBS (14,15,51). Unfortunately, initial contact of nerve fibers with these substances is accompanied by intense pain, and nerve fibers regenerate or regain sensitivity over time, limiting efficacy in some patients and duration of relief of pain subsequent to these treatments in most patients (52,53).

Release of substance P, neurokinin A, and CGRP has been associated with smooth muscle contraction, vasodilation, increased vascular permeability, and facilitated neurotransmitter release from intramural nerves in the bladder wall (54,55). Some of these effects are a direct result of interaction with specific receptors for these neuropeptides on the vasculature or smooth muscle, but many are the result of stimulation of release of prostaglandins, bradykinin, and cytokines from leukocytes and other cells. There is a reciprocal release of mediators of pain and inflammation in response to neuropeptides entailing subsequent further release of neuropeptides in response to these noxious substances, suggesting a circular, self-perpetuating process that leads to persistence of pain and inflammation after the initial insult has resolved (56-59). It is assumed that, under normal circumstances, homeostatic mechanisms act to limit this cyclical process, but it is possible that suppression or loss of homeostatic mechanisms could result in chronic pain and inflammation of the bladder or other organs.

Mast cells appear to play a particularly crucial role in neurogenic inflammation. Mast cells have received particular attention in studies of IC/PBS in humans because they are present in increased numbers within the bladder wall in at least a subset of these patients (60-62). Mast cells have also been observed in close contact with sensory nerves within the bladder wall (63-66). Mast cells synthesize and release a number of vasoactive and chemotactic factors, including histamine, prostaglandins, leukotrienes, serotonin, bradykinin, tumor necrosis factor-α, and platelet activating factor (67-69). Degranulation resulting in release of pro-inflammatory factors by mast cells typically occurs subsequent to crosslinking of antigen with immunoglobulin bound to the surface of the mast cell, and this is referred to as immediate or Type I hypersensitivity (70). However, non-immunologic stimuli such as substance P, bradykinin, tumor necrosis factor-α, and nerve growth factor also have the capacity to stimulate release of mast cell contents (68,69). We have previously reported that experimental cystitis induced in mice by intravesical instillation of substance P or E. coli lipopolysaccharide was far less severe in mice that were genetically deficient in mast cells compared to that observed in congenic wild-type mice (71).

Initiating factors for neurogenic inflammation vary widely and include antigens, cold, heat, bacterial or viral infection, or direct stimulation of nerves (43-45). Models of antigen- and viral-induced cystitis will be discussed in this section.

Antigen-Induced Cystitis

Exposure of the airways of sensitized guinea pigs to antigen has long been used as a model to study airway disease and asthma (72). Experimental cystitis induced by systemic sensitization of guinea pigs to ovalbumin and subsequent intravesical instillation of this antigen was described in 1991 (73). Intravesical instillation of ovalbumin into the bladders of naïve guinea pigs has no effect. Since this model is dependent on a Type I hypersensitivity response, mast cells clearly play a crucial role in development of cystitis. This model was adapted for use in mice, and it was demonstrated that intravesical instillation of antigen consistently caused cystitis in wild-type control mice, but not in mice rendered genetically deficient of mast cells (74).

Multiple studies have demonstrated an integral role for neurogenic-mediated processes in models of antigen-induced cystitis. Exposure of bladder tissue from sensitized guinea pigs to antigen resulted in release of neuropeptides, whereas treatment of bladder tissue from naïve guinea pigs with antigen failed to stimulate neuropeptide release (56). The neurokinin-1 receptor (NK-1) is the primary receptor mediating the direct effects of substance P in neurogenic inflammation (75). Stimulation of NK-1 located on postcapillary venules has been demonstrated to increase vascular permeability, resulting in edema (42,76,77). Significantly, absence of functional NK-1 receptors prevented antigen-induced cystitis in mice, suggesting that activation of NK-1 by substance P is an essential component of antigen-induced cystitis (78). Incubation of bladder tissue from sensitized guinea pigs with antigen also stimulates release of prostaglandins, leukotrienes, histamine, and bradykinin (59,79,80). Absence of antigen-induced cystitis in mice lacking functional NK-1 receptors provides strong evidence that neurogenic inflammation plays a key role in this model of cystitis (78).

Advantages of antigen-induce cystitis primarily relate to avoiding the need to instill infectious or noxious substances systemically or intravesically and the fact that the mechanisms underlying development of bladder inflammation entail intrinsic immune and neurological responses. It has also been noted that patients with IC/PBS have a relatively higher incidence of allergies and asthma than the general population (81). However, disadvantages of this model arise primarily from the lack of clear evidence for a similar pathogenesis in patients with IC/PBS.

Viral-Induced Cystitis

It was observed in 1997 that injection of modified pseudorabies virus into the abductor caudae dorsalis tail muscles of the rat caused hemorrhagic cystitis that was prevented by denervation of the bladder (82). The importance of the role of the CNS in this process was further confirmed by results of experiments by this group demonstrating that lesions of areas of the spinal cord (bilateral dorsolateral or ventrolateral funiculectomy) or brainstem (lesions of Barrington's nucleus/locus coeruleus area) associated with innervation of the bladder prevented cystitis subsequent to injection of virus into the tail muscles (83). Further studies using this model in mice demonstrated that release of pro-inflammatory and nociceptive substances by mast cells in the lamina propria of the bladder resulted in pain, inflammation, and loss of barrier function of the urothelium (84-87). Referred somatic pain induced by viral cystitis in mice was suppressed by antagonists of the NK-1 or histamine-2 receptors (84). These investigators further reported that the cytokine tumor necrosis factor-α may play a key role in migration of mast cells into the bladder wall (87).

Subsequent to injection into the tail muscles, the virus was only cultured from the spinal cord, not the bladder or urine (86). Histologically, virus was observed in the superficial layers of the dorsal horn of the thoracolumbar and sacral spinal cord, as well as the brainstem (83,88). Combined, these results strongly suggest that the effects of injection of virus into the tail muscles is dependent upon irritation of the relevant areas of the CNS resulting in release of neuropeptides and ingress of mast cells within the bladder wall. While this model demonstrates that innervation of the bladder has the capacity, when stimulated appropriately, to cause cystitis, its utility, as with most other models of bladder disorders in humans is limited to confirming the capacity of potential mechanistic pathways to participate in the onset and persistence of bladder disorders.

Autoimmune Cystitis

Around 40 years ago, it was suggested that self-antibodies directed against the bladder could be the cause of IC/PBS (89), and other investigators have subsequently reported findings

suggesting that chronic autoimmune disorders may be the underlying cause of some bladder disorders in humans (90-93). These observations are particularly intriguing in light of the higher incidence of autoimmune disorders (e.g., rheumatoid arthritis, Sjogren's Syndrome, systemic lupus erythematosis, and others) in patients diagnosed with IC/PBS than that observed in the general population (94-97).

Experimental cystitis has been induced in mice (98-100) and rats (101) by injection of homogenized bladder tissue obtained from syngeneic rodents combined with adjuvant. Cystitis in these animals is characterized by increased urinary frequency and decreased voiding volume. Histologically, bladders in sensitized animals typically exhibited increased vascularity, increased numbers of leukocytes within the bladder wall, increased permeability to ^{14}C-urea, and occasional mucosal ulceration (98-101). Interestingly, cystitis was induced by adoptive transfer by intraperitoneal injection of naïve mice with suspensions of homogenates of spleen and lymph nodes obtained from sensitized mice (98) and rats (101). The successful induction of cystitis by adoptive transfer demonstrates that capacity of primed immune cells to recognize and respond to normal bladder tissue.

Autoimmune cystitis was also induced by generation of transgenic mice in which the urothelium expressed ovalbumin (OVA) as a result of insertion of the gene sequence for OVA driven by the uroplakin II gene promoter (102,103). The transgenic mice (Tg-OVA) did not exhibit spontaneous cystitis, but intravenous injection of $CD8^+$ T cells obtained from Tg-OVA mice that had been incubated in vitro with an OVA peptide consistently induced cystitis. Creation of double-transgenic Tg-OVA mice that expressed $CD8^+$ T cells that were responsive to OVA resulted in mice that spontaneously developed cystitis.

These studies, in combination with clinical observations, strongly support the possibility that autoimmunity plays a significant role in IC/PBS. Unfortunately, direct support for this in the form of identification of one or more antigens that specifically stimulate cystitis in patients is still lacking. The role of autoimmunity in the pathogenesis of IC/PBS is further confounded by a lack of reports that imunosuppressive therapy prevents or diminishes symptoms of IC/PBS. However, it is still possible that an autoimmune response may trigger a series of events that results in persistent symptoms of IC/PBS in the absence of an active autoimmune reaction.

Cytitis Induced by Irritants

Experimental cystitis has been induced by intravesical instillation of a variety of irritants, including bacterial lipopolysaccharide (LPS), acid, turpentine, mustard oil, croton oil, and acrolein. Systemic treatment of rodents with cyclophosphamide is one of the most common methods used to initiate cystitis. Cyclophosphamide is an antineoplastic agent, and hemorrhagic cystitis is a common complication observed in patients treated with this drug. Cyclophosphamide is metabolized by the liver to acrolein, and the presence of acrolein within the bladder is thought to be the cause of cystitis in patients or animals that receive cyclophosphamide (104,105). Chemical irritants, including cyclophosphamide or acrolein, directly damage the urothelium and other cells of the bladder, resulting in varying degrees of erosion of the mucosa, edema, hemorrhage, and leukocytic infiltration of the bladder wall.

Exogenous irritants have been used to induce inflammation of the bladder in rats and mice to create cystitis to investigate mechanisms underlying pain and inflammation associated with cystitis. The advantage of these models is that they allow control of the timing, duration, and severity of inflammation. It is also possible to investigate various strategies intended to diminish the severity of pain and inflammation in these controlled models. Unfortunately, studies that investigate treatment options are typically designed to administer the particular intervention being evaluated prior to initiation of bladder inflammation. While this may

imply efficacy in patients that have intermittent cystitis, these results may or may not be applicable to patients who have established inflammation at the time of examination and treatment. Other disadvantages of these models primarily relate to whether or not the mechanisms that underlie the response of the bladder and nervous system to these compounds are relevant to those that result in inflammation and associated pain in patients with cystitis.

E. coli LPS is the bacterial product most commonly instilled into the bladder to initiate cystitis. Instillation of E. coli LPS alone into the bladders of mice stimulates cystitis characterized by edema, hemorrhage, and infiltration of neutrophils into the bladder wall (106), and there is evidence that LPS may cross the bladder wall, enter lymphatics or blood vessels, and ultimately be deposited in other organs, including the lungs and rectum (107). In rats, protamine sulfate is typically instilled into the bladder to destroy the glycosaminoglycan layer prior to infusion of LPS to induce cystitis (108-111). Interestingly, systemic administration of E. coli LPS by intraperitoneal or intravenous injection also stimulates inflammation of the bladder in rats and mice characterized primarily by edema within the bladder wall (71,108,112). The toll-like receptor 4 (TLR4) is thought to be the transmembrane receptor responsible for cellular response to LPS (113,114), and instillation of uropathogenic E. coli into the bladders of mice that spontaneously express dominant negative TLR4 (C3H/HeJ mice) resulted in bacterial colonization of the bladder wall in the absence of inflammation (115).

Bacillus Calmette-Gueirin (BCG), prepared from an attenuated strain of Mycobacterium bovis, was initially used as a vaccine against tuberculosis (116). BGG is now commonly instilled into the bladder to treat superficial, noninvasive cancer (117). It has recently been reported that instillation of BCG into the bladders of mice stimulates profound inflammation (118).

A survey of relevant literature suggests that the vast majority of experimental studies of the onset and sequela of cystitis utilize exposure of the bladder to irritant chemicals. It was reported over 20 years ago that intravesical instillation of turpentine, mustard oil, or croton oil stimulated cystitis characterized by edema, hemorrhage and leukocytic infiltration of the bladder wall (119). Bladder inflammation has also been induced by intravesical administration of hydrochloric (120,121) or acetic (122,123) acid in rats and mice. These models consistently produce cystitis and damage to the urothelium that is accompanied by activation of a variety of signaling pathways too numerous to summarize in this review (29,124-129) .

Hemorrhagic cystitis has been reported as a complication of treatment of patients with cyclophosphamide since the mid-1960's (130). Systemic treatment of rodents with cyclophosphamide as a model to induce cystitis has been used for at least 40 years (131) and is one of the most common experimental models of bladder inflammation. Cyclophosphamide has not been reported to stimulate inflammation of other organs of the urinary tract (132), and, as mentioned previously, its irritant effects on the bladder have been attributed to contact of the bladder surface with acrolein.

Direct instillation of acrolein into the bladder has been shown to induce cystitis (133,134). This model has the potential advantage relative to systemic administration of cyclophosphamide of not requiring hepatic metabolism of cyclophosphamide to acrolein, and at least one study reported differential rates of metabolism of cyclophosphamide and subsequent excretion of acrolein into the urine by two strains of mice (135). We investigated cystitis induced by intravesical instillation of acrolein in mice to determine whether or not the severity of cystitis could be more tightly controlled and also whether or not differences

in response to acrolein could be detected among strains of mice (Figure 1) (136). We found that the intensity of inflammation could be varied in direct proportion to the concentration of acrolein instilled, and we also observed that, when identical volumes and concentrations were administered intravesically, acrolein-induced cystitis was more severe in C57bl/6n and C3H/OuJ mice than in C3H/HeJ mice. Part of the motivation for performing this study was the concern that the severity of cystitis induced by some models could be so severe that subtle differences in signaling or response to potential therapeutic interventions could be overwhelmed by massive tissue damage and inflammation. The results of this study indicate that strains of rats and mice, as well as the intensity of inflammation induced, should be considered when selecting models of cystitis to investigate mechanisms underlying bladder inflammation or response to various interventions.

Prostatic inflammation

Benign prostatic hyperplasia (BPH) affects more than 50 percent of men past the age of 50, and as many as one-third of all men develop significant BPH-related lower urinary tract symptoms (LUTS) that require treatment (137). LUTS include increased urinary frequency, urgency, nocturia, weak urinary stream, straining to void, and a sense of incomplete emptying, and the incidence of LUTS increases with age in men (138). Historically, LUTS in men with BPH have been attributed to physical obstruction of the bladder outflow tract by prostatic encroachment on the urethral lumen (139-142). However, in a recent study of men with LUTS, half the study population (42/84) had no evidence of bladder outlet obstruction (143), and it has been proposed that LUTS associated with benign prostatic hyperplasia (BPH) are actually the result of 3 components: prostatic enlargement, alpha-adrenergic receptor-mediated narrowing of the urethra, and prostatic inflammation (144). In a retrospective study of 3,942 prostatic biopsies from BPH patients, inflammation (primarily chronic inflammation) was observed in 1,700 (43.1%) (8). Inflammation was observed in all histological specimens obtained from 80 men without symptoms of prostatic inflammation who underwent transurethral prostatectomy for treatment of BPH, suggesting that inflammation is extremely common in patients with symptoms of BPH who have no other symptoms of prostatic inflammation (9).

A role for bacterial colonization or infection in the etiology of BPH is plausible but remains controversial. Analysis of material obtained by biopsy of the prostate using the polymerase chain reaction (PCR) demonstrated the presence of bacterial 16S ribosomal RNA, suggesting the presence of bacteria in prostates with histological evidence of inflammation (145,146). Bacteria were also cultured from 38% of tissue samples obtained by transurethral prostatectomy from patients who had negative urine cultures prior to surgery (147). It also appears that urinary reflux into the prostatic ducts is a common occurrence (148) and bacterial colonization/infection in surgical specimens of BPH may be more common than previously assumed.

It has also been suggested that prior infection or the presence of normal commensal organisms may sensitize afferent innervation of the prostate, contributing to prostate-associated pain (149). One of the co-authors (WB) has previously described a model of prostatic inflammation that was induced by a single transurethral inoculation with E. coli 1677 (150). This strain of E. coli was isolated from a patient with a severe urinary tract infection (151). Twelve week old male C3H/HeOuJ (OuJ) mice were anesthetized, a urethral catheter was inserted, and bacteria (2×10^6 CFU) in a 20 μl volume were instilled. Mice were sacrificed 5 days and 12 weeks after instillation of bacteria. Histology of the prostate 5 days after instillation of bacteria demonstrated edema, shedding of epithelial cells, and infiltration of neutrophils into the stroma and ducts (Figure 2). Prostate glands removed from mice sacrificed 12 weeks after infection had varying degrees of atypical hyperplasia, dysplasia,

epithelial proliferation, lymphocytic infiltration, and evidence of oxidative DNA damage. Instillation of phosphate-buffered saline had no effect on prostate histology.

We have since modified the protocol to include treatment of mice with nitrofurantoin (3.4 mg/kg, sc, twice daily) for 1 day prior and daily for 3 days after instillation of bacteria to prevent bacterial cystitis. Mechanical sensitivity of the hind paws was assessed in these mice using von Frey monofilaments to investigate the effects of prostatic inflammation on referred mechanical hypersensitivity. Our preliminary data indicate that a single infusion of E. coli resulted in localized prostatic infection and inflammation and increased sensitivity to application of mechanical stimuli to the hind paws (unpublished observations).

These results indicate that this may be a useful model of prostatic inflammation. They further suggest that prostatic inflammation has the capacity to sensitize the afferent nervous system, providing support for the notion that LUTS associated with prostatic inflammation could be due to neural plasticity induced by inflammation of the prostate.

Summary

A wide variety of animal models of inflammation of the lower urinary tract has been used over an extended period of time. The principal benefits of this research relative to lower urinary tract inflammation in humans relate to potential mechanisms underlying the onset and persistence of pain and inflammation. With the exception of disorders arising from bacterial causes, initiating causes of inflammatory diseases in humans remain obscure. Unfortunately, no currently-available animal model, including infection models, perfectly mimics disease that occurs in humans. These models have therefore have mainly been of benefit in identifying potential mechanisms underlying clinical disease. Further comparative and translational studies are required to better characterize causes of clinical disease in humans and the utility of animal models in studying these causes.

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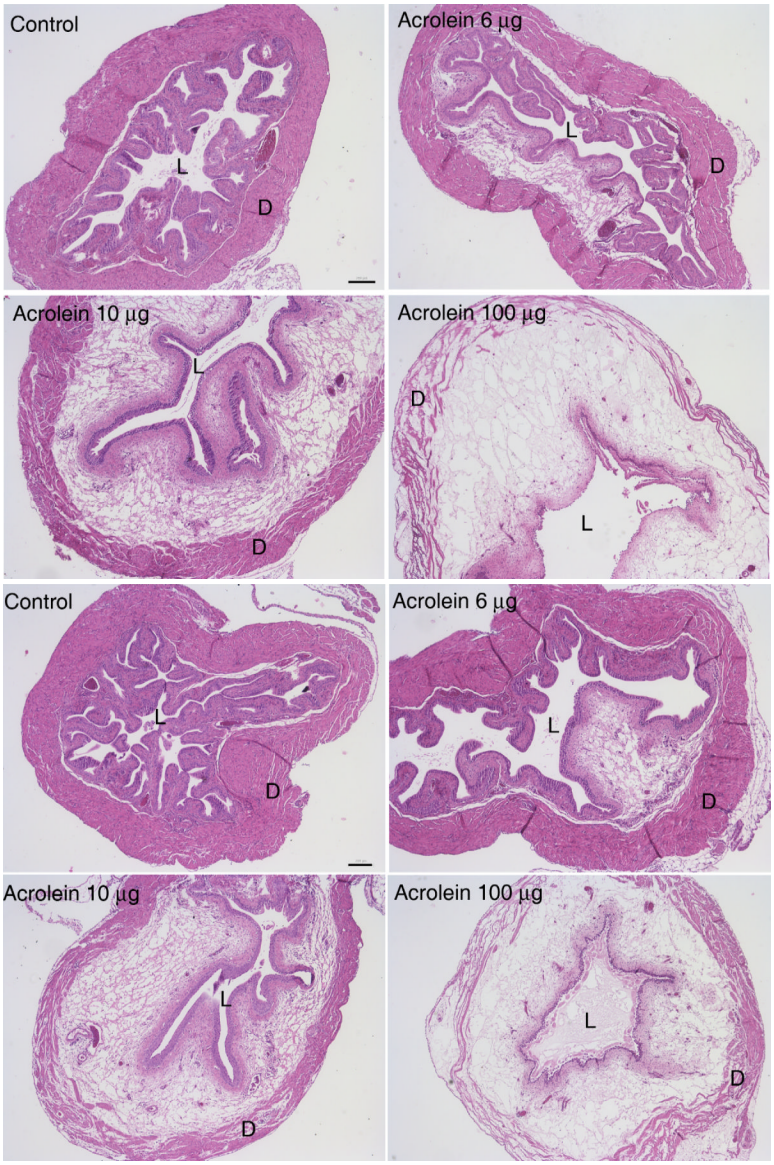
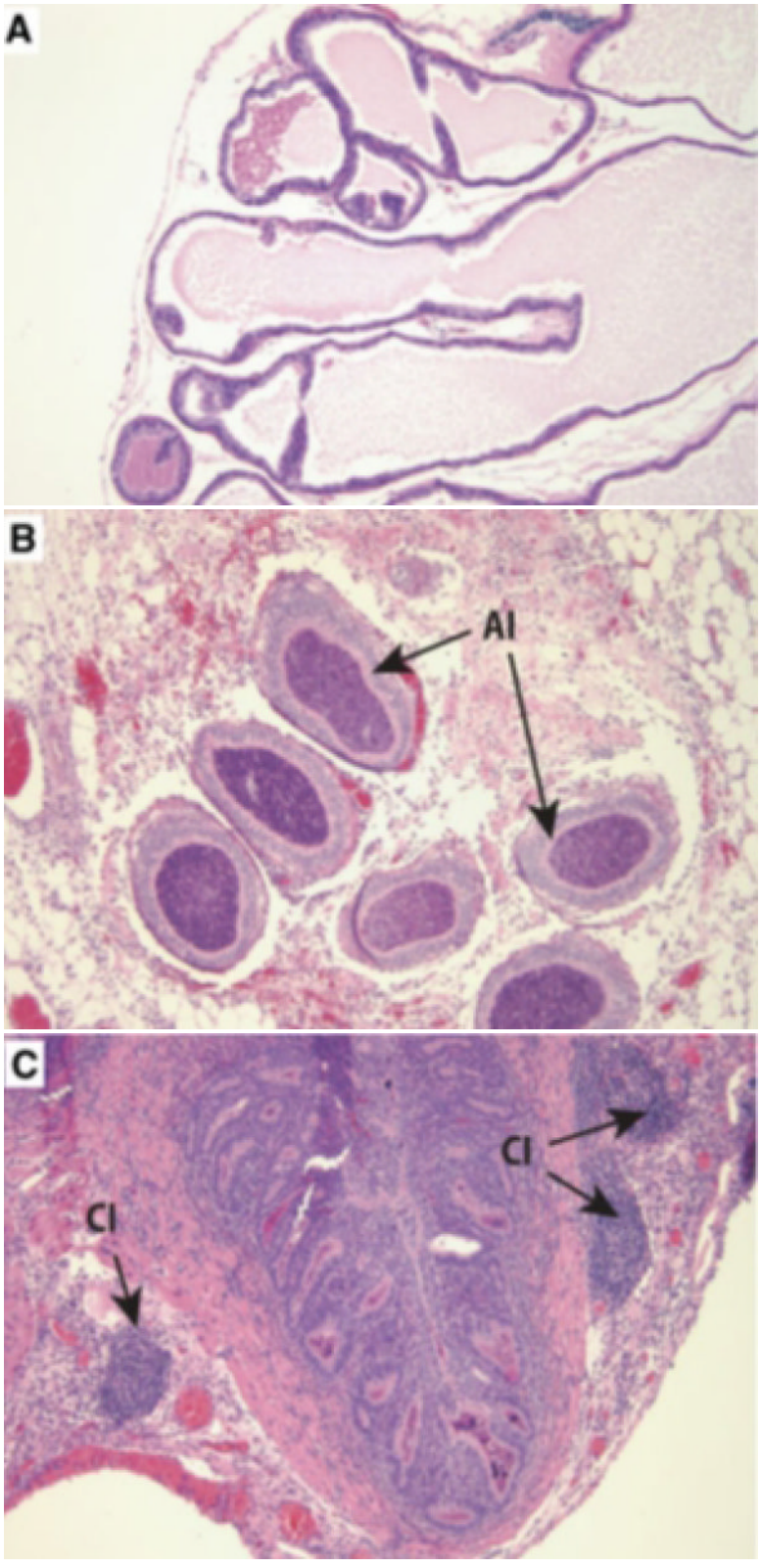


Figure 1.

Four (A) and 24 hours (B) after instillation of acrolein (6, 10, or 100 µg; 15 µl total volume) or 15 µl phosphate buffered saline (PBS; control) into the bladders of female C57BL6N mice, it was observed that the severity of inflammation as indicated by intramural edema and hemorrhage correlated with increasing concentrations of acrolein. (L, lumen; D, detrusor); 40x original; scale bar = 200 µm. (With permission from: Bjorling DE, Elkahwaji JE, Bushman W, Janda LM, Boldon K, Hopkins WJ, Wang ZY. Acute acrolein-induced cystitis in mice. BJU Int 2007;99:1523-1529.)



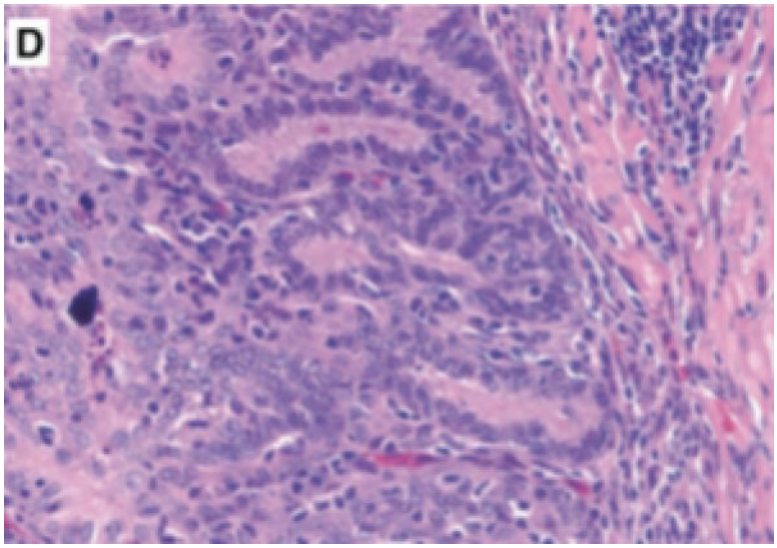


Figure 2.
Prostatic inflammation was induced by a single transurethral instillation of E. coli 1677 in C3H/OuJ mice as previously described (141). A. Instillation of saline failed to cause any histological response when tissues from mice sacrificed 5 days after infusion were stained with hematoxylin and eosin. B. Five days after instillation of E. coli 1677, evidence of acute inflammation (AI) characterized by edema, inflammatory cell infiltrate, and exfoliation of epithelial cells into the ducts was observed. C. and D. Chronic inflammation (CI) consisting of dense accumulation of lymphocytes was present in the coagulating gland 12 weeks after instillation of bacteria, as well as evidence of early dysplastic changes in the ductal wall (D). 10x original. (With permission from: Elkahwaji JE, Zhong W, Hopkins WJ, Bushman W.Chronic bacterial infection and inflammation incite reactive hyperplasia in a mouse model of chronic prostatitis. Prostate 2007;67:14-21.)

Table 1

Animal Models of Lower Urinary Tract (LUT) Inflammation

Cause of LUT Inflammation	Species	Advantages	Disadvantages	References
Spontaneous Inflammation	Cats	Develops without external intervention	Etiology remains unknown	19–28,35,36,39
Neurogenic Inflammation	Mice, Rats, Guinea Pigs	Viral model results in inflammation without external manipulation of the bladder	Difficult to be certain that inflammation solely arises from activation of nerves	41–50,54–59,65, 71,73–75,78 80,82 - 88
Autoimmunity	Mice, Rats, Guinea Pigs	IC/PBS patients have a high co-morbidity of immune-related disease	Target(s) of immune response in bladder remain uncertain	94,98-103
Intravesical Instillation or Urinary Excretions of Irritants	Mice, Rats	Can control severity and duration of inflammation	Causes indiscriminate damage to glycosaminoglycan layer, urothelium, and wall of bladder by multiple mechanisms	16,17,104,105,119 – 136,
Intravesical Instillation of Bacterial Products	Mice, Rats	Bacterial infection occurs naturally in humans	Difficult to recapitulate genetic and environmental factors influencing response of bladder	12,13,106,107– 115, 118,
Transurethral Instillation of Bacteria into the Prostate	Mice	Consistently produces acute or chronic inflammation	Role of infection remains unclear in BPH, prostatic pain, or prostatic inflammation in patients	150