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Invited review

Pathology, pathophysiology, and pathogenesis of painful bladder diseases

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Introduction

Definitions and clinical findings

The painful bladder disease complex includes a large group of urological patients with pain in the bladder, irritative voiding symptoms (urgency, frequency, nocturia, dysuria) and sterile urine. There are painful bladder diseases with a well known etiology and pathogenesis (i.d. irradiation cystitis, cyclophosphamide cystitis, cystitis caused by specific microorganisms, carcinoma in situ, malacoplakia and systemic diseases affecting the bladder), and many other painful bladder diseases with an unknown etiology [32]. It is the latter group which concerns this review.

This large group, mostly of female patients, have caused concern to urologists for many years. [68]. Few specific diagnostic criteria are established for the condition and since the etiology and pathogenesis are unknown no rational therapy exists [10].

The patients present with a variety of urological symptoms in a more or less severe degree: suprapubic pain, sensory urgency, dysuria and daily and nigthly urinary frequency. There might also be hematuria or strangury [19]. The urine is sterile and cytologically normal. A cystoscopy under local anaesthesia is often quite normal, but sometimes an increased vascularisation on a pale mucosa or an ulcer is seen [14]. A cystoscopy under general anaesthesia with bladder distension at maximal capacity at a pressure of 80 cm H_2O for 1 min often reveals petechial or ecchymosal bleeding after emptying of the bladder, which some consider diagnostic for the disease [56]. The bladder capacity measured at cystoscopy is variable. The majority have a quite normal bladder capacity, but some have a small contracted bladder and others a large dilated bladder.

Scarring and ulcers of the mucosa are still a matter of discussion. Sometimes a true "Hunner's ulcer" can be observed. It is very important not to confuse an old scar from a biopsy with a lesion secondary to the disease (an ulcer). Hunner's "elusive ulcer" is described as a superficial shallow linear crack or scar surrounded by small dilated blood vessels which bleed on distension [34]. In our institution we consider it as a very rare finding (1–5%) [29]. The Swedish group have a different opinion, they simply define patients with classical interstitial cystitis as having an ulcer [12].

Urodynamic studies are never able to prove the diagnosis of painful bladder disease, but they might be very helpful in excluding other bladder diseases and especially to differentiate from neurogenic bladder diseases and "motor-urge-bladders" [58]. Most patients with symptoms from a painful bladder undergo cystometry with measurement of residual urine and flowmetry. Most patients are unobstructed with normal flowrate and no residual urine except for the detrusor myopathy patients, who tend to have large bladders with insufficient emptying. The cystometry is often very unpleasant for the patient as a result of suprapubic pain during filling and severe sensory urgency with a first sensation at low bladder volumes [9]. Bladder capacity measured at cystometry is most often reduced as filling is unterrupted because of pain. This is in contrast to bladder capacity measured at cystoscopy under general anaesthesia, during which the "real" capacity [7, 29] is found. At the end-stage of interstitial cystitis with a small contracted bladder, and a low capacity during cystoscopy under general anaesthesia, the characteristic low compliance bladder can be diagnosed.

The majority of the patients with painful bladder disease do not exhibit uninhibited detrusor contractions, but the demonstration in the cystometrogram of uninhibited detrusor contractions, does not exclude the painful bladder diagnosis.

An interesting new urodynamic study of 32 interstitial cystitis patients assess ed the response to medical

therapy (DMSO) [63]. They found the most useful parameters to be volume at first sensation and maximum cystometric capacity during medium flow cystometry. If the patients improved the volumes increased.

Finally urodynamic studies are necessary if open surgical procedures are needed [44, 58].

To define and classify the painful bladder patients of unknown etiology and pathogenesis, we have used the findings from deep bladder biopsies ie, a bladder biopsy including the detrusor muscle [19].

In conjunction with the cystoscopy under anaesthesia a bladder biopsy and urine cytology should be taken, to rule out carcinoma in situ and bladder cancer [42]. The biopsy in painful bladder patients is most often abnormal. In our study we found an abnormal bladder biopsy in 111 of 115 patients [29].

For classification in our institution we deal with the following pathoanatomic diagnosis: interstitial cystitis, detrusor myopathy, chronic unspecific cystitis and eosinophilic cystitis [25, 26, 29, 32].

Pathology

Interstitial cystitis

Interstitial cystitis (IC) is associated with a pancystitis [8, 13, 43, 66]. There is a thinning of the mucosal lining, sometimes the mucosa is detached, but the urothelium is always normally differentiated. If an ulcer is present the area is covered by a layer of fibrin mixed with erytrocytes and leucocytes [8, 13]. The mucous surface coat (glycosaminoglycans or GAG-layer) cannot be evaluated properly by light microscopy. The lamina propria is oedematous, congested and contains dilated capillaries and perivascular hemorrhages. There is a difffuse cellular infiltration throughout the bladder wall mainly with lymphocytes but neutrophils and eosinophil granulocytes, plasma cells and mast cells are also present. Collagen is distributed between the muscle fascicles (interfascicular) and as a special feature in IC, also within the muscle fascicles (intrafascicular) [43]. Severe degrees of fibrosis give rise to small contracted bladders. The muscle cells themselves in IC are normal. In small lacunae between the muscle cells, mast cells are found in increased numbers [15, 43, 51], and at our institution we have used that as a diagnostic criteria for IC. We have concluded that patients with more than 28 mast cells per mm^2 detrusor muscle (detrusor mastocytosis) [41] and painful bladder symptoms have interstitial cystitis. In our control series of patients with stress incontinence as the only urological symptom, only few mast cells are counted [7].

Controversial in IC-patients is whether mast cells were present in the lamina propria in an increased number. The reports are conflicting and the question is not yet solved [6, 15, 43, 51]. Recently a study by Aldenborg, Fall and Enerbäck, where two types of mast cells in the bladder were reported, made the confusion about the mast cells and IC even worse [1]. Two types of mast cells exist, the connective tissue or serosal mast cell and the mucosal mast cell. Beside their different location these mast cells differ in biochemical composition and function [11]. The differentiation between the two types of mast cells by light microscopy is difficult and requires a special technique [1]. Aldenborg reported that mucosal mast cells after migration from the lamina propria might be present in the urothelium in IC patients and suggests that the mucosal mast cells IgE-system might be involved in the etiology and pathogenesis of IC [1]. The same group also found mast cells in bladder washings from IC patients and proposed this as a diagnostic test [14].

The nerves in the bladder wall have never been systematically investigated in IC patients. Some authors describe fibrosis around the nerve fibers in the detrusor muscle as characteristic of IC [66] while others describe perineural inflammatory cell infiltration as an outstanding feature [13].

There are few electron microscopic studies of the bladder in painful bladder patients. Dixon's study with Ruthenium red from 1986 tries to rule out possible differences in the urothelium and mucous surface coat between IC patients and controls (stress incontinence patients) [7]. It was uncertain whether IC patients lacked the mucous surface coat (GAG-layer) or not [61]. The EM-study revealed no differences in the GAG-layer and ultrastructure of the urothelium between IC patients and controls. Two types of luminal cells were observed. One cell type had numerous plaques of asymmetric unit membrane associated with a relatively thin glycocalyx, the other cell type possessed numerous microvilli and a thicker glycocalyx. This was considered an age phenomenon and is in agreement with other studies in elderly patients.

Collan also reported a normal ultrastructure of the urothelium in IC patients [4].

Fine structural studies of bladder submucosal vessel walls from patients with IC have demonstrated pronounced vascular injury in approximately 70% of cases [53]. Severely damaged endothelial cells are commonly observed together with proliferation and multilayering of the underlying basal lamina. This lamina is sometimes destroyed by polymorphonuclear cells and the subendothelial space is relatively wide and oedematous. In 75% of the vascular smooth muscle cells, small spherical membranebound vesicles (granulovesicular bodies) associated with elastic elements occupying the intermuscular spaces of the blood vessel wall, are found. These vesicles are believed to be associated with

both regenerating and newly developing elastic elements (microfibrils) [53]. The microfibrils may act as antigens in the pathogenetic process, and the subsequent injury to the vessel may be due tu autoantibodies or to immune complexes formed within them.

Detrusor myopathy

Our pathologist observed certain changes in the detrusor muscle cells in some of the biopsis from the painful bladder patients. Looking again in these patients medical records there appeared to be some clinical differences. [27]. The pathoanatomic findings in these detrusor myopathy patients include a normally differentiated urothelium, a mononuclear cell infiltration in the lamina propria and muscle coat and some fibrosis. The dominant microscopic findings are changes in the detrusor muscle cells themselves that might be of a degenerative nature. The changes includes hydropia of the muscle cells, perinuclear vacuolization, karyopyknosis, and even karyorrhexis. In some patients a fatty replacement of the muscle tissue is seen within the muscle fascicles. We have observed in some detrusor myopathy patients a perineural cell infiltration.

The ultrastructural studies of the muscle cell changes in the patients with detrusor myopathy reveal a decreased cytoplasmic density and the formation of large perinuclear vacuoles in the muscle cell [2, 27] indicating degeneration of the cell.

Chronic unspecific cystitis

In some patients with painful bladder symptoms no mast cell infiltration and no muscle changes are seen [13, 29]. In these patients one finds varying degrees of chronic cystitis. The urothelium is still normally differentiated, but might be detached and ulcerated, in parts the lamina propria is oedematous and infiltrated with mononuclear cells and granulocytes. In the muscle coat varying degrees of interfascicular fibrosis are present. The changes are very nonspecific and vary in severity.

Eosinophilic cystitis

Some patients, often with very severe symptoms and petechial or diffuse bleeding on bladder distension, have a marked infiltration of eosinophil cells throughout the whole bladder wall. Otherwise the microscopic appearance is as in chronic unspecific cystitis. In fulminant cases the changes are so severe that even muscle cell necrosis is present [24].

Pathophysiology

Having classified the painful bladder patients by the pathoanatomical criteria described, it seems that certain clinically defined patient groups appear [25].

The patients with interstitial cystitis tend to have more pain and frequency, more severe petechial bleedding and a smaller bladder capacity than the patients with detrusor myopathy, who tend to complain of stranguria, residual urine and even urinary retention and have larger bladders. The patients with chronic nonspecific cystitis might exhibit every characteristic of the disease and are the most difficult to recognize from the clinical symptoms. The patients with eosinophilic cystitis often have a fulminant course and might have episodes of generalised illness.

It is questionable whether it is right to classify the patients pathoanatomically since an unpublished study, in which we rebiopsied the patients at varying intervals showed that even with the same clinical symptoms the pathology might change in the same patient with time. Futher studies are in progress to clarify the problem.

Pathogenesis

The etiology and pathogenesis of painful bladder disease are still obscure [32]. Many theories exist including infection, toxic agents in the urine, genetic or endocrinologic deficiencies, lymphatic or vascular obstruction, neurogenic, allergic or immune causes and defects in the cytoprotection of the bladder or even psychiatric disease. All these theories are reviewed by Messing [57].

It is now generally accepted that painful bladder disease is not one disease, but rather a symptom complex, or syndrome. There might be more than one etiologic factor responsible for the pathoanatomical appearence and the different symptoms, and treatment ought not to be the same for the different patients. The most predominant theories today are illustrated in Table 1: A substance in the urine, either a substance occurring in normal urine (a foodstuff, a metabolite etc.) and only harmful to particularly susceptible bladders, or a substance not occurring in normal urine (a toxic agent) gain access to the bladder wall. This happens either through a defective glycosaminoglycans-layer (GAG-layer) or by destroying a normal GAG-layer, implying an easier penetration of the urothelium, since the natural cytoprotection of the bladder is impaired. The urothelium itself might be abnormally leaky. In the bladder wall inflammatory changes are induced, either toxically, allergically or immunologically. These changes might also be induced

Table 1. Theories on the etiology and pathogenesis of painful bladder disease.

Urine	GAG-Layer Urothelium	Bladder wall
an agent in the urine	quantitatively and/or qualitatively defective GAG-layer	toxic, allergic or immunologic induced inflammatory reactions
	Ulcers Vulnerable urothelium Petechial bleeding	Patho-anatomic abnormalities in the bladder (Interstitial cystitis Detrusor myopathy Eosinophilic cystitis Chronic unspecific cystitis)

by a blood borne agent, but it is reasonable to believe that urine plays a role, since patients with urinary diversions are relieved of their bladder symptoms [46].

Much research has been done to try to find the etiologic agents to painful bladder disease. Numerous studies failed to demonstrate bacterial, viral and fungal infections as causative for IC [20, 23]. Hunner originally proposed that IC was a result of chronic bacterial infection of the bladder. A new interesting study proposed that anaerobic bacteria adherent to the vesical wall and which are very difficult to culture by conventional methods may be involved in the pathogenesis [52].

Recently herpes simplex virus in the bladder was investigated but the result was negative [13]. In a report on Epstein-Barr virus [17] it was found that 118 of 150 patients with IC had a marked elevation of certain anti-capsid antigen antibodies in the blood.

Antibiotics have been proposed as being able to induce IC, but it has not been convincingly proved [16, 45].

That degranulation of mast cells with subsequent release of mediators play a role in the pathogenesis of the disease in at least mastocytosis patient (IC) is accepted. It is still completely inknown what might cause degranulation.

It is logical to assume that urine is involved and a study using epicutaneous reactions with urine was performed [3]. The study showed that patients with IC had a high incidence of positive skin reactions to patch tests with urine compared to controls. The positive reactions were primarily seen to the patients own urine, but also, although less frequently to foreign urine. Immediate skin reactions were not seen. The morphology and histology of the positive patch tests suggested a toxic rather than an allergic reaction. These data support the assumption that urine contains a substance that elicits a probably toxic reaction in IC-patients. This factor is found in increased amounts in urine from IC-patients and these patients furthermore have a decreased threshold to the component, possible due to a defective mucous layer of the bladder. The mucous surface coat with its content of glycosaminoglycans lining the urothelium is thought to play a role in the cytoprotection of the bladder [62] and acts as an important defence mechanism between the urothelial cells and bacteria and other harmful substances in the urine [22]. Glycosaminoglycans (GAG's) were earlier called acid mucopolysaccharides and they are mainly distributed in the matrix of the connective tissue all over the body, but the presence of GAG's on cell surfaces have now been demonstrated in several systems [39]. GAG's are extremely hydrophilic because of their negatively charged compounds, and are therefore capable of forming a barrier between the surface and the environment [18]. Parsons was the first who draw attention to the relationship between IC and the GAG-layer [61]. It was hypothezised that IC-patients lacked the GAG-layer, but a morphological study denied that [7]. Later it appears that both qualitative and quantitative deficiencies in the GAG-layer might be present. A decreased urinary excretion of GAG's in patients with IC compared to controls has been shown [35, 38]. The same authors proposed some interesting theories based on quantitative differences between ureteral and bladder urine in IC-patients and hypothezised that exogenous GAG's from the kidneys might "patch" damaged areas on the bladder urothelium. That urinary GAG's might be able to bind tightly at a mucous deficient urothelium was confirmed in later studies [37], which also showed a quite different GAG-composition in surface coat compared to the GAG isolated from the whole bladder.

Qualitative studies on the GAG-layer with lection probes have shown that carbohydrate terminals of the bladder surface GAG's are unchanged in patients with IC, but that the biochemical composition of the different GAG's are altered (more galactose and fucose in IC-patients) [65].

In a recent preliminary study we investigated the qualitative differences in the mocous surface coat of the bladder between IC-patients and controls [28]. By a new cystoscopic scraping method the mucous surface coat including the GAG's were collected in a buffer and analysed by electrophoresis. We found that IC-patients had a higher percentage of hyaluronic acid and dermatan sulfate in the mucous surface coat than did controls (prostatic hypertrophy). The patients had a lack of heparan sulfate which is known to be the major GAG on cell surfaces [5].

If quantitative changes in the GAG-layer are involved in the pathogenesis of IC it is logical to hypothezise that the urothelial cells are producing less GAG's. EGF (epidermal growth factor or urogastrone) is a growth promoting hormone, playing a role in cytoprotection and the production of GAG's in the gastrointestinal tract. We investigated the urinary excretion of EGF in IC-patients but found no changes in the urinary excretion when compared to normal, age-matched controls [30].

In the bladder wall in patients with painful bladder disease various inflammatory processes are taking place. The exact nature of these processes still remain unclear. We do not know what initiates and starts the chronic inflammatory response.

In the IC-patients with mast cells in the bladder it is reasonable to believe that they play a role and by an unknown mechanism are attracted to the bladder wall. In the other painful bladder patients the inflammatory reaction does not involve mast cells. In the detrusor myopathy patients muscle cell degeneration is induced, also by unknown mechanisms. In eosinophilic cystitis a fulminant allergic reaction involving the eosinophils is seen. In chronic nonspecific cystitis the reactions in the bladder wall do not suggest any particular mechanism of induction. When mast cells degranulate different mediators are released: histamine, prostaglandins, chemotactic factors, leucotriens, heparin etc. Recently many studies have been done in IC-patients trying to monitor the inflammatory response by measuring the mediators or their derivatives. When eosinophilic chemotactic factor is released by the degranulating mast cells, eosinophils are mobilized to the inflammatory site, where they modify the inflammatory response through deposition of granule products including eosinophil cationic protein (ECP) and/or phagocytosis of mast cell granules [67]. An increased number of eosinophils in bladder biopsies from patients with IC is found together with an increased concentration of ECP in urine [47–49], compared to patients with chronic nonspecific cystitis. ECP might be responsible for the maintenance of the inflammatory process and the tissue destruction in IC.

An elevated urinary excretion of a metabolite of histamine, 1,4-methyl-imidazole-acetic-acid (1,4-MIAA) has also been demonstrated in IC-patients [31], as is an elevated concentration of histamine in bladder biopsies [41, 50]. Another mediator from mast cell degranulation, prostaglandin E2, has also been found in elevated urinary concentration in IC-patients [50].

Autoimmune reactions might explain many facets of IC and have been proposed to initiate the inflammatory reaction [60]. The pathological findings, the chronic but relapsing course of the disease and certain immunological studies speak for that. On the contrary, the way these patients respond to immunosuppression and anti-inflammatory drugs speaks against it [57]. Also the recurrence of IC in colocystoplasties [55] and the disappearance of symptoms after urinary diversion without cystectomy [46], argues against the autoimmune theory. Studies be the Finnish group suggest that activation of complement is involved [53, 54]. The association of IC with connective tissue diseases, especially lupus erythematosus, has also been speculative [40, 59, 69]. In many ways IC resembles a local manifestation of lupus but there is no evidence for a systemic connective tissue disease.

Further immunologic studies eventually with isolation of mast cells to study degranulation are necessary to clarify the exact nature of the inflammatory processes in the bladder wall.

Painful bladder disease with its few objective findings have commonly among urologists been considered as a psychiatric disease [21]. We performed a study of 33 patients with painful bladders, where a psychiatric interview and a MMPI (Minnesota Multiphasic Personality Inventory) were employed [33]. The study showed, that these patients exhibited a wide spectrum of psychic abnormalities (only 25% normal). We did not find any difference between the patients with and without an elevated mast cell count in the detrusor and no correlation between the severity of the psychic abnormality and the severity of the bladder symptoms, the duration of the disease and the existance of a psychotrauma. Since the psychiatric abnormalities in painful bladder patients agreed with the findings in patients with chronic organic pain (cancer), we concluded that the psychic abnormalities are more likely to be caused by the chronic pain and voiding symptoms rather than being responsible for them.

Conclusion

Many unresolved questions remain regarding painful bladder disease. The etiology, pathogenesis and pathophysiology are not precisely known and therefore no rational therapy exist. One have to keep in mind that the lack of efficient therapy is the main problem for these, often very disabled and handicapped patients [64]. The goal for all future research regarding painful bladder patients has to be to find an efficient and rational therapy.

References

1. Aldenborg F, Fall M, Enerbäck L (1985) Proliferation and transepithelial migration of mucosal mast cells in interstitial cystitis. Immunology 58:411–416

2. Barnard RJ, Dixon JS, Gosling JA (1987) Myopathy of detrusor smooth muscle. Br J Urol 59:595–596
3. Clemmensen O, Lose G, Holm-Bentzen M, Colstrup H (1988) Skin reactions to urine in patients with interstitial cystitis. Urology 32:19–20
4. Collan Y, Alfthan O, Kivilaakso E, Oravisto KJ (1976) Electron microscopic and histological findings in urinary bladder epithelium in interstitial cystitis. Eur Urol 2:242–247
5. Comper WD, Laurent TC (1978) Physiological function of connective tissue polysaccharides. Physiol Rev 58:225–316
6. Deane AM, Parkinson MC, Cameron KM, Hindmarsh JR (1983) Mast cells in female sensory bladder disorders. Proceedings of the International Continence Society, Annual Meeting, Aachen, p 51
7. Dixon JS, Holm-Bentzen M, Gilpin CJ, Gosling JA, Bostofte E, Hald T, Larsen S (1986) Electron microscopic investigation of the bladder urothelium and glycocalyx in patients with interstitial cystitis. J Urol 135:621–625
8. Dixon J, Hald T (1986) Morphological studies of the bladder wall in interstitial cystitis. In: George NJR, Gosling JA (eds) Sensory disorders of the bladder and urethra, chapt 7. Springer, Berlin Heidelberg New York, p 63
9. Dunn M, Ramsden PD, Roberts JBM, Smith JC, Smith PJB (1977) Interstitial cystitis treated by prolonged bladder distension. Br J Urol 49:641–645
10. Editorial (1988) Painful bladder diseases: interstitial or abacterial cystitis? Lancet I:337
11. Enerbäck L (1981) The gut mucosal mast cell. Monogr Allergy 17:222–232
12. Fall M (1985) Conservative management of chronic interstitial cystitis: Transcutaneous electrical nerve stimulation and transurethral resection. J Urol 133:774–778
13. Fall M, Johansson SL, Vahlne A (1985) A clinico-pathological and virological study of interstitial cystitis. J Urol 133:771–775
14. Fall M, Johansson SL, Aldenborg F (1987) Chronic interstitial cystitis: a heterogeneous syndrome. J Urol 132:35–38
15. Feltis JT, Perez-Marrero R, Emerson LE (1987) Increased mast cells of the bladder in suspected cases of interstitial cystitis: a possible disease marker. J Urol 138:42–43
16. Gillespie LM, Said J, Cain D, Van der Veld R (1985) Antibiotic-induced interstitial cystitis: a model for cell membrane instability. Proceeding of the International Continence Society, Annual Meeting, London, p 254
17. Gillespie LM, Jones JF (1986) Epstein-Barr virus infection and interstitial cystitis: the rosetta stone of inflammatory disease? J Urol 135–271
18. Gregor HP (1975) Anticoagulant activity of sulfonate polymers and copolymers. In: Gregor HP (ed) Polymer science and technology, vol 5. Plenum Press, New York, p 51
19. Hald T, Holm-Bentzen M (1986) Clinical symptom complex. In: George NJR, Gosling JA (eds) Sensory disorders of the bladder and urethra, vol 6. Springer, Berlin Heidelberg New York, pp 49–62
20. Hanash KA, Pool TL (1970) Interstitial and hermorrhagic cystitis: viral, bacterial and fungal studies. J Urol 104:705–706
21. Hand JR (1949) Interstitial cystitis: report of 223 cases (204 women and 19 men). J Urol 61:291–310
22. Hanno PM, Fritz R, Wein AJ, Mulholland SG (1978) Heparin as antibacterial agent in rabbit bladder. Urology 12:411–415
23. Hedelin HH, Mårdh P-A, Brorson JE, Fall M, Møller B, Petterson KGS (1983) Mycoplasma hominis and interstitial cystitis. Sex Transmitt Dis 10:327–330
24. Hellström HR, Davis BK, Shonnard JW (1979) Eosinophilic cystitis. A study of 16 cases. Am J Clin Pathol 72:777–785
25. Holm-Bentzen M, Hald T, Larsen S (1984) An attempt to classify patients with painful bladder by histology. Abstract, 6th Congress of the European Association of Urology, Copenhagen, Denmark, p 38
26. Holm-Bentzen M (1985) Painful bladder: classification of the disease. Scand J Urol Nephrol [Suppl] 94:10
27. Holm-Bentzen M, Larsen S, Hainau B, Hald T (1985) Non-obstructive detrusor myopathy in a group of patients with chronic abacterial cystitis. Scand J Urol Nephrol 19:21–26
28. Holm-Bentzen M, Ammitzbøll T, Hald T (1986) Glycosaminoglycans on the surface of the human urothelium: a preliminary report. Neurourol Urodyn 5:519–523
29. Holm-Bentzen M, Jacobsen F, Nerstrøm B, Lose G, Kvist Kristensen J, Pedersen RH, Krarup T, Feggetter J, Bates P, Barnard R, Larsen S, Hald T (1987) Painful bladder disease: Clinical and pathoanatomical differences in 115 patients. J Urol 138:500–502
30. Holm-Bentzen M, Lose G, Jørgensen L, Sørensen K, Nexø E (1987) Chronic cystitis: excretion of epidermal growth factor (EGF)/urogastrone (URO). Urol Res 15:203–205
31. Holm-Bentzen M, Søndergaard I, Hald T (1987) Urinary excretion of a metabolite of histamine (1,4-methyl-imidazole-aceticacid) in painful bladder disease. Br J Urol 59:230–233
32. Holm-Bentzen M, Lose G (1987) Pathology and pathogenesis of interstitial cystitis. Urology [Suppl] 29:8–13
33. Holm-Bentzen M, Christensen JK, Lieth L, Hald T (in press) Psychiatric and psychological evaluation of patients with painful bladder. Neurourol Urodyn
34. Hunner GL (1915) A rare type of bladder ulcer in women: report of cases. Boston Med Surg J 172:660–664
35. Hurst RE, Roy JB, Bynum RL, Parry WL (1985) Abnormal glycosaminoglycans excretion in patients with chronic interstitial cystitis. J Urol 133:144
36. Hurst RE, Parsons CL, Roy Jb (1986) The mechanisms for low glycosaminoglycans excretion in interstitial cystitis and mechanisms for protection of bladder from urine. J Urol 135:189
37. Hurst RE, Rhodes SW, Adamson PB, Parsons CL, Roy JB (1987) Functional and structural characteristics of the glycosaminoglycans of the bladder luminal surface. J Urol 138:433–437
38. Hurst RE, Roy JB, Desai S, Parsons CL (1988) Urinary glycosaminoglycans excretion as a diagnostic test for interstitial cystitis. J Urol 139:276
39. Höök M, Kjellèn L, Johansson S, Robinson J (1984) Cell surface glycosaminoglycans. Ann Rev Biochem 53:847–869
40. Jokinen EJ, Alfthan OS. Oravisto KJ (1972) Antitissue antibodies in interstitial cystitis. Clin Exp Immunol 11:333–339
41. Kastrup J, Hald T, Larsen S, Nielsen VG (1983) Histamine content and mast cell count of detrusor muscle in patients with interstitial cystitis and other types of chronic cystitis. Br J Urol 55:495–500
42. Lamm DL, Gittes RF (1977) Inflammatory carcinoma of the bladder and interstitial cystitis. J Urol 117:49–51
43. Larsen S, Thompson SA, Hald T, Barnard RJ, Gilpin CJ, Dixon JS, Gosling JA (1982) Mast cells in interstitial cystitis. Br J Urol 54:283–286
44. Leach GE, Raz S (1983) Interstitial cystitis. In: Raz S (ed) Female urology. Saunders, Philadelphia 351
45. Levin RM, Lavkar RM, Monson FC, Witowski BA, Wein AJ, Hanno PM, Ruggieri MR (1988) Effect of chronic nitrofurantoin on the rabbit urinary bladder. J Urol 139:400–404
46. Linder CH, Smith RD (1958) Hunner's ulcer. Br J Urol 30:338–342
47. Lose G, Frandsen B, Højensgaard JC, Jespersen J, Astrup T (1983) Chronic interstitial cystitis: increased levels of eosinophil cationic protein in serum and urine and an ameliorating effect of subcutaneous heparin. Scand J Urol Nephrol 17:159–161
48. Lose G, Jespersen J, Frandsen B, Højensgaard JC, Astrup T (1985) Subcutaneous heparin in the treatment of interstitial cystitis. Scand J Urol Nephrol 19:27–29

49. Lose G, Frandsen B, Holm-Bentzen M, Larsen S, Jacobsen F (1987) Urine eosinophilic cationic protein in painful bladder disease. Br J Urol 60
50. Lynes WL, Shortliffe LD, Flynn SA, Zipser R, Roberts J (1986) Mast cell involvement in interstitial cystitis. J Urol 135:272
51. Lynes WL, Flynn SD, Shortliffe LD, Lemmers M, Zipser R, Roberts LJ, Stamey TA (1987) Mast cell involvement in interstitial cystitis. J Urol 138:746–752
52. Maskell RM (1985) Chronic interstitial cystitis. Lancet I:394
53. Mattila J, Pitkänen R, Vaalasti R, Seppänen J (1983) Fine-structural evidence for vascular injury in patients with interstitial cystitis. Virchows Arch [A] 398:347–355
54. Mattila J, Linder E (1984) Immunoglobin deposits in the bladder epithelium and vessels in interstitial cystitis: possible relationship to circulating antiintermediate filament autoantibodies. Clin Immunol Immunopathol 3:81–89
55. McGuire ES, Lytton B, Carnog SL (1973) Interstitial cystitis following colocystoplasty. Urology 2:28–29
56. Messing EM, Stamey TA (1978) Interstitial cystitis, early diagnosis, pathology and treatment. Urology 12:381–392
57. Messing EM (1986) Interstitial cystitis and related syndromes. In: Walsh PC, Gittes RF, Perlmutter AD, Stamey TA (eds) Campbell's urology, 5th edh. Saunders, Philadelphia, p 1070
58. Messing EM (1987) The diagnosis of interstitial cystitis. Urology [Suppl] 29:4–7
59. Oravisto KJ, Alfthan OS, Jokinen EJ (1970) Interstitial cystitis, clinical and immunological findings. Scand J Urol Nephrol 4:37–42
60. Oravisto KJ (1980) Interstitial cystitis as an autoimmune disease. A review. Eur Urol 6:10–13
61. Parsons CL, Greenspan C, Moore SW, Mulholland SG (1977) Role of surface mucin in primary antibacterial defence of bladder. Urology 9:48–55
62. Parsons CL (1986) Bladder surface glycosaminoglycans: efficient mechanism of environmental adaption. Urology [Suppl] 27:9–14
63. Perez-Marrero R, Emerson L, Juma S (1987) Urodynamic studies in interstitial cystitis. Urology [Suppl] 29:–27–30
64. Ratner V (1987) Rediscovering a "rare" disease: a patient's perspectice on interstitial cystitis. Urology [Suppl] 29:44–45
65. Sant GR, Ucci AA, Alroy J (1986) Bladder surface glycosaminoglycans (GAG's) in interstitial cystitis. J Urol 135–175
66. Smith BH, Dehner LP (1972) Chronic ulcerating interstitial cystitis (Hunner's ulcer). Arch Pathol 93:76–81
67. Venge P, Dahl R, Hällgren R, Olsson I (1980) Cationic proteins of human eosinophils and their role in the inflammatory reaction. In: Mahmoud AAF, Austen KF (eds) The eosinophils in health and disease, chapt 8. Grune and Stratton, New York
68. Wein A (1985) Editorial. Neurourol Urodyn 4:153–155
69. Weisman MH, McDanald EC, Wilson CB (1981) Studies of the pathogenesis of interstitial cystitis, obstructive uropathy, and intestinal malabsorption in a patient with systemic lupus erythematosus. Am J Med 70:875–878

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