JOINT MEETING OF THE 3rd INTERNATIONAL CONSULTATION ON INTERSTITIAL CYSTITIS JAPAN (ICICJ3) AND THE ESSIC ANNUAL MEETING 2013, 21-23 March 2013, Mielparque, Kyoto, Japan

Jane Meijlink

This was the third time that Japan has organised a meeting of world experts in the field of interstitial cystitis/bladder pain syndrome and hypersensitive bladder, held on this occasion in 2013 as a joint meeting with the International Society for the Study of BPS (ESSIC) and with the support of the Society of Interstitial Cystitis of Japan (SICJ) and the Comfortable Urology Network (CUN) of Japan. Many thanks are due to Dr Tomohiro Ueda for once again organising this unique, thought-provoking meeting of experts. A total of 126 delegates from around the world came to Kyoto, with 22 invited speakers in the main programme and 21 speakers presenting posters in the research programme. Two patient representatives were present from Germany (ICA-Deutschland and the IPBF) and several Japanese patient representatives attended. While it was an intensive 2½ day programme, plenty of time was allowed for questions and discussion. It was also the perfect opportunity to learn first-hand about the hypersensitive bladder concept of the East Asian countries Japan, Korea and Taiwan, with a special presentation on this topic by Professor Yukio Homma of Tokyo.
The presentations will be published in a special supplement of the International Journal of Urology scheduled for January 2014.

THURSDAY 21 MARCH

SESSION I: INTRODUCTION, FOCUS AND HISTORY

Dr Tomohiro Ueda opened the conference, noting that the meeting had two main focuses: phenotyping of bladder pain based on pathophysiology and crosstalk between clinical and basic research.
Jane Meijlink (IPBF) then presented an historical setting that looked at interstitial cystitis – a history of nomenclature, definitions and criteria, spanning two centuries.

SESSION II: UPDATE

USA
Philip Hanno, MD updated delegates on the USA situation, reporting that the AUA IC/BPS guideline online has attracted many hits since 2011, indicating great interest and a major continuing impact. It is hoped, he said, that the AUA definition will enable diagnosis to be made sooner with less diagnostic testing in the USA. The potential impact of the AUA Guideline should also include improvement of IC/BPS differentiation from CPPS/nonbacterial prostatitis and increase recognition of IC/BPS in men. This American guideline argues for non-invasive basic assessment, thereby lowering the cost of diagnosis and initial treatment, discouraging the use of the potassium test and thereby eliminating painful, unnecessary testing. It encourages a treatment approach that begins with the most conservative, progressing where necessary to more invasive therapy. It also legitimizes unapproved treatments (non-FDA approved) including cyclosporine and botox and highlights better pain treatment as a priority. It recommends use of symptom scales and pain scales to improve monitoring of patients' response to therapy. The Guideline strongly recommends local therapy for Hunner's lesions. Priority should also be given to self-care, behavioural modification and patient empowerment through education.
Link to AUA Guideline: http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/ic-bps/diagnosis_and_treatment_ic-bps.pdf

Addressing epidemiology in the USA, Dr Hanno looked at the RAND Interstitial Cystitis Epidemiology or RICE telephone survey studies based on self-reported symptoms which indicated that IC/BPS may be very prevalent,

underdiagnosed and undertreated in the USA, based on the RICE High Specificity Definition (Sensitivity 48%, Specificity 83%). They recently published the results of looking at the men in the study, indicating an equally astounding prevalence. **The question is how these figures should be interpreted and whether they are in fact realistic.**

Berry SH, Elliott MN, Suttorp M, Bogart LM, Stoto MA, Eggers P, Nyberg L, Clemens JQ. Prevalence of symptoms of bladder pain syndrome/interstitial cystitis among adult females in the United States. Urol. 2011 Aug;186(2):540-4. Doi: 10.1016/j.juro.2011.03.132. Epub 2011 Jun 16. Free access, click here.

Suskind AM, Berry SH, Ewing BA, Elliott MN, Suttorp MJ, Clemens JQ. The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: results of the RAND Interstitial Cystitis Epidemiology male study. J Urol. 2013 Jan;189(1):141-5. Doi: 10.1016/j.juro.2012.08.088. Epub 2012 Nov 16.

Dr Hanno then discussed treatments available in the USA and their effectiveness as shown in trials, including oral drugs such as PPS (Elmiron): not very promising in recent studies, amitriptyline: possible benefit at higher doses; intravesical therapy in the USA – DMSO and cocktails (cocktail with steroid + heparin): continues to show efficacy up to 6 months, but due to odour cannot be used successfully in randomised trials; lidocaine and cocktails; GAG layer replenishment agents are not in common use in the USA due to non-approval by the FDA, but are commonly used in Europe with success. He concluded that large randomised controlled trials are urgently needed to underline the benefit of this type of therapy. He reported that probably the biggest advance in the past twenty years has been in the field of physical therapy/myofascial trigger point release and intravaginal Thiele massage, based on work by Mary Pat Fitzgerald and the Interstitial Cystitis Clinical Research Network. This is now a standard part of the AUA algorithm and commonly used as a first line therapy in the USA and represents a major change and improvement in therapy.

He took a brief look at The Multidisciplinary Approach to Study of Urologic Chronic Pelvic Pain (MAPP) which is just beginning to bear fruit. The initial 5 year project was completed in February 2013, with massive accumulation of data. A second multiyear project incorporating clinical trials is now in development. He reported that there should be data in the Trans-MAPP epidemiology study available to determine cross-sectional prevalence and to evaluate associations among baseline characteristics of patients with urologic chronic pelvic pain syndromes; the prevalence of associated somatic syndromes and psychological syndromes; the relationship of associated syndromes to symptom duration; comparisons between men and women and comparisons between those with and without pain perceived to be related to the bladder.

In closing, Dr Hanno did not personally feel that a great deal of progress has been made in the past ten years in the field of treatment. However, it is hoped that the data coming from the MAPP can ultimately be translated into better treatment for patients.

EUROPE

Jørgen Nordling, MD from Denmark noted that many problems lie in the fact that everyone has been using different terminology and definitions in their studies and it is unclear on what basis patients in studies have been diagnosed. This creates a lot of problems, he said, because you cannot accurately compare studies.
However, he felt that much had changed since the meeting in Kyoto in 2003. It was clear at that time that there were great differences in different parts of the world, but he felt that these differences are now getting smaller.
He briefly looked at the EAU Guidelines Committee for Chronic Pelvic Pain which was established in January 2002 and produced its first full text CPP guideline in 2003. The third full text was published in 2012. There have been many terminology and definition issues in Europe with both being influenced by the International Continence Society (ICS), the International Association for the Study of Pain (IASP), previous EAU Guidelines and ESSIC. Looking at the description of pain according to the IASP system, he explained that the system followed was: region -> system -> end organ -> referral characteristics -> temporal characteristics -> character.
Diagnosis according to the EAU is on the basis of pain, pressure or discomfort associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and or night-time increased urinary frequency, the exclusion of confusable diseases as the cause of the symptoms, and if indicated, cystoscopy with hydrodistension and biopsy. This is very close to the ESSIC and AUA definitions. The algorithm emphasises diagnosing Hunner's lesion at the earliest stage and if it is present treat it locally with laser or TUR. If not present, start with conservative or oral treatment and progress until the patient has adequate relief. There is

accumulating evidence of central nervous system (CNS) changes and multi-system problems including sensory alterations. The EAU therefore advocates a multidisciplinary approach to the disease.
The ESSIC defines BPS on the basis of chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or urinary frequency. Confusable diseases should be excluded and cystoscopy with hydrodistension might be performed and biopsy. Showing the ESSIC list of confusable diseases, Dr Nordling noted that ketamine-associated cystitis (from recreational use of ketamine) has now been added to this list.

The definition proposed at the Rome discussions on nomenclature and definitions in 2012, attended by experts from Europe, Asia and North America, was that (BPS) would be diagnosed on the basis of a chronic unpleasant sensation (e.g. pelvic pain, pressure or discomfort) perceived to be related to the urinary bladder, generally accompanied by lower urinary tract symptoms. Confusable diseases as the cause of the symptoms must be excluded.
Further documentation and classification of (BPS) might be performed according to findings at cystoscopy with hydrodistension and morphological findings in bladder biopsies.
The presence of other organ symptoms as well as cognitive, behavioural, emotional and sexual symptoms should be addressed.
So this was not very different from previous definitions, except for the East Asian definition with a rather different approach with a specific definition of interstitial cystitis and a hypersensitive bladder concept.

Dr Nordling agreed with Dr Homma from Japan when he says that if patients say they have no pain, you cannot give them a diagnosis of bladder pain syndrome. Dr Nordling suggested that this group of patients should be treated as a special phenotype to see if they fit best within bladder pain syndrome or overactive bladder syndrome or hypersensitive bladder.

Moving on to the controversial issue of glomerulations which have been shown many times in the past to be non-specific, Dr Nordling felt that the best paper on this topic was by Waxman and colleagues showing that 45% of asymptomatic women have bladder findings (glomerulations) identical to patients with IC.
Waxman JA, Sulak P J, Kuehl T J Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation J Urol 1998 Nov;160(5):1663-1667.
Research Posters presented at the meeting also showed that glomerulations were found in patients with BPH, SUI & HSB, stone and other disorders and that patients with upper urinary tract stones also showed glomerulations. Concluding that glomerulations are frequently present in non-IC patients and not present in many IC patients, he therefore emphasised that, while it is unknown what glomerulations mean and how they occur, it is clear that they cannot be used as a diagnostic tool.

Looking at Hunner's lesion, he noted that history has shown us that Hunner's lesions were synonymous with interstitial cystitis (a term introduced in the 19th century) until the mid-20th century. Hunner's lesion has specific cystoscopic and morphological findings and responds well to specific treatment. There was much more on this subject later in the meeting

EAST ASIA
Yukio Homma, MD from Japan reported on developments in East Asia since the previous ICICJ in 2007. This included publication in 2009 of Clinical Guidelines for Interstitial Cystitis and Hypersensitive Bladder Syndrome in which Japan, Taiwan and Korea participated. The definition of IC in these 2009 guidelines is based on: a symptom complex with increased sensation, frequency, discomfort, pain (hypersensitive bladder symptoms); bladder pathology (Hunner's lesion or mucosal bleeding post-distension); exclusion of other diseases.
Clarifying their use of the term hypersensitive bladder, he explained that patients without pain are not uncommon; non-pain symptoms also cause great bother, and may in fact cause the most bother, and are frequently present. We should not forget, he said, that the urothelium is a very sophisticated sensory tissue. The term hypersensitive bladder has been seen in a number of recent scientific papers and goes back to the 1988 ICS definition. He also pointed out that IBS which bears great similarity to IC is not a pain syndrome.
In the algorithm he showed us, hypersensitivity included frequency, urgency, discomfort or pain. Cystoscopy plays a key role in East Asian diagnosis. Dr Homma also emphasized the importance of identifying Hunner's

lesion, describing it as a reddish erosive lesion, linear rather than spheroid in shape, with fibrin clots on the surface, radiating vessels and/or scars in the vicinity and easily haemorrhagic and painful. He also stressed that atypical lesions can easily be overlooked without intentional search and may be accompanied by massive bleeding after hydrodistension. He showed standardised drawings of hypervascularity, scar, biopsy, glomerulations, rainy bleeding, waterfall bleeding, Hunner's lesion and crack or fissure which are included in the Asian guidelines. He discussed the use of onabotulinumtoxin-A injections in Taiwan, adding that they have found it significantly better for non-lesion type and that it can have a good effect on pain. But it was found that 3-4 repeated injections are better than a single one only and lead to a longer term effect.

On gene expression in interstitial cystitis, he reported that they have explored genetic alterations in the bladder tissue of IC/BPS patients and their major finding is that a number of genes related to sensation and inflammation are upregulated almost exclusively in classic IC. Major findings include:

- Classic IC (lesion type): increased mRNA expression of TRP family (A1, M2, M8, V1, V2), ASIC1 and CXCL9. -> Pronococeptive inflammatory reactions
- Non-classic IC (non-lesion): increased mRNA expression of NGF

He concluded by saying that classic IC and non-classic IC have distinct etiology, with classic IC featuring more pronounced pronociceptive inflammation. In practical assessment, he emphasized that special attention should be paid to non-pain symptoms and Hunner's lesions. Working is continuing in this field in East Asia and more publications are in the pipeline.

Discussion: should the name interstitial cystitis be reserved for Hunner's lesion?
A discussion followed about Hunner's lesions in which Dr Nordling suggested that we should think about reserving the name interstitial cystitis for the Hunner's lesion type since it would be historically correct and where the patients and patient associations are concerned would preserve the name IC. Should it be a sub-group of BPS or a separate disease? One delegate preferred to stay with BPS and the ESSIC subtype 3C. Dr Fall said he thought it would be appropriate to use the term IC for Hunner's lesion, but a problem could arise in that IC had now come to mean more. Dr Whitmore said that names such as IC should not be discarded until we know exactly what we are talking about and are sure that everyone is on the same page.
Dr Hanno had seen patients with sudden, very red and seriously inflamed bladders that didn't seem to be IC, but he didn't know what it was. Dr Fall had also seen this phenomenon. Discussion also concerned the question of whether there is progression from non-lesion to lesion. While some clinicians have seen cases of apparent progression, they said it might be that they had missed the lesion initially.

SESSION III: RELATED SYMPTOMS AND DISEASES – SIMILARITIES AND DIFFERENCES

Unfortunately two speakers from this session were unable to attend due to illness. Speaking on immunological diagnosis of bladder pain syndrome/interstitial, **Dr Ueda** looked at current knowledge regarding peripheral targets and mechanisms underlying IC/BPS, and therapeutic strategies, reporting that Narrow Band Imaging (NBI) and the Neurometer can play an important role in clarifying the immunological condition of the urinary bladder. He concluded by saying that immunological reactivity may be an important component in the pathogenesis of IC/BPS, resulting in hypersensitivity of the urinary bladder to physical and chemical stimulation.

Mauro Cervigni, MD from Rome discussed gynaecological effects and pelvic floor dysfunction in IC/BPS patients, looking at associated gynaecological disorders. He described IC/BPS as a gender disease since it affects more women than men, and explained that this is one of the big mysteries of the syndrome. Gynaecologic associated conditions include: vulvodynia, endometriosis, pelvic floor dysfunction, recurrent UTI, and he said he would like to add pudendal neuropathy here, even though it is considered a confusable disease, and emphasised that it was important for clinicians dealing with IC/BPS patients to know more about pudendal neuropathy. On the subject of vulvodynia, he explained that this term was recommended in 2001 by the International Society for the Study of Vulvar Disease (ISSVD), instead of the term vestibulitis, so as to eliminate any inflammatory or infective implication. The ISSVD definition of vulvodynia is: "vulvar discomfort, most often described as burning pain (present for at least 3 months), occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder". On the topic of embryology, and referring to a paper

by Fitzpatrick et al, 1993, he noted that because both the vestibule of the vulva and the bladder are derived from the urogenital sinus, the coexistence of the vulvar pain and interstitial cystitis in some patient represents a generalised disorder of urogenital sinus-derived epithelium. Both vulvodynia and IC/BPS, he said, are associated with increased capillary growth or angiogenesis. This angiogenesis seen through the cystoscope in IC/BPS patients represents the same eythematous areas seen in the vestibule of vulvodynic patients. Reflex sympathetic dystrophy, postulated to occur in IC/BPS, has also been studied in vulvodynia, where dilated inflamed blood vessels are thought to release chemical stimulators of sympathetic nerve fibres in vessel walls. (*Stewart E, Berger B, 1997*). IC/BPS can also appear concurrently with endometriosis and there is indeed a high prevalence of association between IC/BPS and endometriosis. Study data have shown that it is important to consider the bladder as the source of pain, even when endometriosis has been diagnosed. Pelvic floor dysfunction symptoms include pelvic pain, urinary urgency and frequency, pain with sexual intercourse or orgasm, variable or intermittent urinary flow rate, constipation and lower back pain. Many IC/BPS patients also have hypertonic pelvic floor dysfunction (HPFD) with muscle tenderness and spasm and myofascial pain syndromes often with leg or groin pain. Various terms are seen for pudendal neuropathy, including pudendal nerve entrapment (entrapment only), pudendal canal syndrome (Alcock's canal only) and pudendal neuralgia (pain only). Pudendal neuralgia is a functional entrapment of the pudendal nerve. The main symptom is pain aggravated by sitting or exercise, voiding, defecating, ejaculation, vaginal penetration, orgasm.

Yasuhiko Igawa, MD from Tokyo, kindly stepping in for Professor Wyndaele who was unable to attend due to illness, then looked at the similarities and differences between OAB and IC/BPS, focusing on clinical definitions, diagnostic approaches and treatment. Looking at definitions of OAB, neurogenic bladder, IC, PBS, BPS and HSB and definitions of urgency, Dr Igawa said the situation was rather confusing! There is indeed a grey area, he said, where the distinction between OAB and IC/BPS becomes a relevant and clinically important problem affecting a substantial number of patients. There is at the present time no gold standard test to differentiate between OAB and IC/BPS. Clinical history, cystoscopic findings after hydrodistension, and detrusor overactivity on UDS may often coincide. History and physical examination can help to differentiate types of urgency and pain, leading to improved diagnostic rates, but there is sometimes overlapping due to difficulty in diagnosis, while IC with mild symptoms may be difficult to differentiate from OAB.

The last speaker in this session was **Michael Pontari, MD** from the USA, with a presentation on infection/inflammation. Patients with IC/BPS do not by definition have an ongoing infection in the bladder. However, because the symptoms are so similar, it is confusing for patients and clinicians alike. There have been many studies searching for infectious organisms in IC. Looking at the impact of bacteria on symptoms of IC, he reported that it has been shown (Nickel et al, 2010) that IC patients with bacteriuria do not differ from those without in terms of age, symptoms, duration or symptom assessment. It was also found that bacteriuria episodes are not associated with flares and antibiotic treatment did not significantly change symptoms. Dr Pontari therefore concluded that the symptoms of IC are not the same as those of acute bacterial infection. Warren J et al, 2000 looked at what happens when you treat patients with antibiotics. They tried 3 weeks each of 6 antibiotics plus 18 weeks of Rifampin. They found overall improvement in 48% of the antibiotic group, and 24% in the placebo group and concluded that use of antibiotics may "sometimes be associated with decreased symptoms." So, he asked, what is the role of infection if there is no ongoing infection at diagnosis, no fastidious or unique organism, antibiotics have mixed results and bacteriuria is not associated with symptoms? *[Comment: many IC/BPS patients may be surprised to read this, since many may indeed have experienced exacerbation of IC symptoms when infection occurred].* Dr Pontari felt that there was still a role since we know from past studies that IC patients are twice as likely to have had a urinary tract infection and that they may have used significantly more antibiotics in childhood. Another question that has been asked (*Warren et al, 2008*) is whether a urinary tract infection was present at the onset of symptoms. They found that 18-36% had evidence of UTI at the onset of their IC symptoms. A study by Arya *et al*, 2011 found that women with a history of recurrent UTI were left with bladder oversensitivity leading to greater urinary frequency. The question then arises as to whether IC/BPS is a (post) infectious disease, he said and whether it depends on the quality and nature of the bacteria concerned and the host, and how many episodes of infection. On the basis of genetics, some patients may be more vulnerable to developing oversensitivity than others. Furthermore, organs outside the bladder may have an influence. It is also necessary to look at loss of barrier function associated with inflammation.

SESSION IV-1 POSTER PRESENTATION & DISCUSSION –CLINICAL- "GENERAL AND EVALUATION"

LESSONS LEARNT IN 20 YEARS OF IC. Nagendra Nath Mishra, India

A STUDY OF INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME BY ANALYZING ITS CLINICAL COURSE. Masaharu Nanri et al, Japan

COMPARISON OF PAIN BETWEEN BLADDER PAIN SYNDROME AND FIBROMYALGIA BY THE DEVICE FOR QUANTITATIVE ANALYSIS OF PERCEPTION AND PAIN SENSATION. Yuki Sekiguchi et al, Japan

THERAPEUTIC EFFICACY OF NARROW BAND IMAGING-ASSISTED TRANSURETHRAL ELECTROCOAGULATION FOR ULCER-TYPE INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME. Mitsuru Kajiwara et al, Japan

DEVELOPMENT AND EVALUATION OF AN E-HEALTH SYSTEM FOR CARING PATIENTS WITH INTERSTITIAL CYSTITIS/ PAINFUL BLADDER SYNDROME. Huei Ching Wu et al, Taiwan

THE CORRELATION OF URINARY BLADDER WEIGHT AND FEMALE INTERSTITIAL CYSTITIS/ PAINFUL BLADDER SYNDROME(IC/PBS). Ming Huei Lee et al, Taiwan

DEVELOPMENT OF BLADDER GLOMERULATIONS AFTER HYDRODISTENSION IN PATIENTS WITH UPPER URINARY TRACT UROLITHIASIS SUGGESTING CROSS TALK AND BLADDER INFLAMMATION OCCUR BETWEEN UPPER AND LOWER URINARY TRACT. Yuan-Hong Jiang et al, Taiwan

REVISIT POTASSIUM SENSITIVITY TEST – A SYSTEMATIC STUDY OF ITS ROLE ON LOWER URINARY TRACT SYMPTOMS. Yuh-Chen Kuo et al, Taiwan

ARE GLOMERULATIONS AFTER CYSTOSCOPIC HYDRODISTENTION A PATHOGNOMONIC SIGN FOR INTERSTITIAL CYSTITIS? Yuh-Chen Kuo et al, Taiwan

THE EFFECTS OF NON-BLADDER COMORBID CONDITIONS ON URODYNAMIC CHARACTERISTICS OF THE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME. Yu-Hua Fan et al, Taiwan.

SESSION IV-2 POSTER PRESENTATION & DISCUSSION CLINICAL "TREATMENT"

INTRAVESICAL ONABOTULINUM TOXINA INJECTIONS DO NOT BENEFIT PATIENTS WITH ULCER TYPE INTERSTITIAL CYSTITIS. Jia-Fong Jhang et al, Taiwan

REPEAT ONABOTULINUM TOXIN-A INJECTIONS PROVIDE BETTER THERAPEUTIC RESULTS THAN SINGLE INJECTION IN TREATMENT OF PAINFUL BLADDER SYNDROME. Jia-Fong Jhang et al, Taiwan

THE USE OF MIRABEGRON FOR URINARY URGENCY AND FREQUENCY ASSOCIATED WITH INTERSTITIAL CYSTITIS: EARLY EXPERIENCE OF FIVE CASES. Akira Nomiyaet al, Japan

EFFECTS OF COMBINATION TREATMENT OF INTRAVESICAL RESINIFERATOXIN INSTILLATION AND HYDRODISTENTION IN PATIENTSWITH REFRACTORY PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS: A PILOT STUDY. Hoon Ah Jang et al, Korea

HOW TO IMPROVE EFFICACY OF INTRAVESICAL INSTILLATION THERAPY? ADVANTAGES OF THE NOVEL METHOD OF HIGH PRESSURE INTRAVESICAL DRUG DELIVERY. Sandor Lovasz et al, Hungary

THE USE OF TRAMADOL FOR REFRACTORY INTERSTITIAL CYSTITIS: RETROSPECTIVE ANALYSIS OF FIFTEEN CASES. Aya Niimi et al, Japan

THE NEED OF HOLISTIC CARE IN WOMEN WITH INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME (IC/PBS) WHO HAVE CHILD ABUSE EXPERIENCE AND PSYCHIATRIC TROUBLES. Wei Chih Tony Chen et al, Taiwan

EFFICACY AND SAFETY OF AUGMENTATION ILEOCYSTOPLASTY WITH SUPRATRIGONAL CYSTECTOMY FOR THE TREATMENT OF REFRACTORY INTERSTITIAL CYSTITIS. Hyung Joon Kim et al, Korea

RELAXING CYSTOPLASTY IN INTERSTITIAL CYSTITIS Nagendra Nath Mishra et al, India

BALLOON DISTENSION OF THE BLADDER INSTEAD OF HYDRODILATION: WHAT ADVANTAGES ARE TO BE EXPECTED? Sandor Lovasz et al, Hungary

AUTOMATIC EVALUATION OF PRESSURE-VOLUME RELATION MEASURED DURING BALLOON- AND HYDRODILATION OF THE BLADDER IN BPS/IC PATIENTS. Sandor Lovasz et al, Hungary

CHEMODENERVATION OF HUNNER LESIONS AS A TREATMENT FOR INTERSTITIAL CYSTITIS / BLADDER PAIN SYNDROME. Kristene Whitmore et al, USA.

FRIDAY 22 MARCH

SESSION V: HUNNER'S LESION

Philip Hanno, MD was the first presenter of the second day, looking at Definitions and Terminology: Bladder Pain Syndrome and Hunner's Lesion. He looked back at the ICICJ meeting in 2003 and the Diokno workshop on the definition. There was, for example, consensus that the classic symptom complex of pelvic pain, urgency and urinary frequency were essential ingredients when suspecting IC. A patient description of discomfort, pressure or burning sensation would suggest pain and support a diagnosis of IC. Workshop 8 (Jurjen Bade) in 2003 noted that there were at that time no classification criteria to differentiate between OAB and IC. He then looked at the different definitions and terminology, with changes from IC to PBS to BPS, noting that at a meeting in 2007 of the Association of Reproductive Health Professionals in the USA, held as a reaction to the ESSIC proposals to change the name and definition, it was stated that patient groups specifically want urge/urgency included in the definition, and the majority at the meeting saw no compelling reason for a name change. An internet survey of 2347 patients showed that 93.2% said NO to a name change, while 97.8% felt that the IC patient community deserved to have a voice in this decision-making process, which it was not getting at the time. Dr Hanno concluded from this that there is still much work to do in involving stakeholders in these processes.

Nomenclature at present in Europe:
ESSIC: Bladder Pain Syndrome
International Consultation on Incontinence: Bladder Pain Syndrome
EAU Guideline: Bladder Pain Syndrome or Painful Bladder Syndrome (former preferred for taxonomy reasons, with IC reserved for a subset of patients with verified signs of chronic inflammation extending submucosally.

Nomenclature in the USA:
AUA Guideline: Interstitial Cystitis/Bladder Pain Syndrome IC/BPS, no distinguishing between the two names, to be used together.

Nomenclature in East Asia: Japan/Korea/Taiwan
Hypersensitive Bladder (HSB), Painful Bladder Syndrome/bladder pain syndrome and Interstitial Cystitis.

Hunner's lesion
Hunner's Lesion is considered to be a vulnus or weakness in the bladder wall rather than a true ulcer. The following descriptions were given:

ESSIC: Hunner's lesion or "ulcer" is a distinctive inflammatory lesion presenting a characteristic deep rupture through the mucosa and submucosa provoked by bladder distension. Despite the name that has been commonly used, it is not an ulcer.

AUA Guideline: The only consistent cystoscopic finding that leads to a diagnosis of IC/BPS is that one or several inflammatory appearing lesions or ulcerations as initially described by Hunner (1918). These lesions may be identified in an acute phase (as an inflamed, friable, denuded area) or a more chronic phase (blanched, nonbleeding area).

Description by Magnus Fall: Hunner's lesion typically presents as a circumscript, reddened mucosal area with small vessels radiating towards a central scar, with a fibrin deposit or coagulum attached to this area. This site ruptures with increasing bladder distension, with petechial oozing of blood from the lesion and the mucosal margins in a waterfall manner. A rather typical, slightly bullous edema develops post-distension with varying peripheral extension.

This was followed by a presentation by **Jørgen Nordling, MD** who looked at diagnostic methods, overview and standardisation. Interstitial cystitis implies that the entire interstitial tissue is involved. He noted that in 1878, Skene discussed inflammation of the bladder, using the term interstitial cystitis and referring to "destruction of portions of the mucous membrane by ulceration". However, he said, this description doesn't fit very well with many of the patients with bladder pain syndrome, only those with lesions. Hunner misinterpreted what he saw as being ulcers, due to poor vision of the inside of the bladder in the early days of cystoscopy. With regard to diagnosis, biopsy is recommended if in doubt as to whether it could be carcinoma in situ (CIS) rather than Hunner's lesion. Looking at a number of specific cases, he reported that he finds lesions in 30% of his patients while Dr Magnus Fall finds them in 50%. He showed us cystoscopies in these patients and treatment of the lesions, explaining that if you can find the lesions, you can really do something to improve life for these patients. There are areas with mucosal ulceration and degenerative urothelial changes including vacuolisation and detachment. Inflammatory infiltrates with varying density is a constant finding. Lymphocyte-like cells dominate in the infiltrate but neutrophilic and eosinophilic granulocytes as well as plasma cells and mast cells are also found. There is perineural and perivascular arrangement of lymphocyte-like cell infiltrates. Granulation tissue is a characteristic finding.

Fall et al. A clinicopathological and virological study of interstitial cystitis. J Urol. 133:771-773, 1985
Johansson et al. Clinical features and spectrum of light microscopic changes in interstitial cystitis. J Urol. 143(6):1118-24,1990.

He also noted that there are high concentrations of Nitric Oxide (NO) in the bladders of lesion patients, but that NO appears to be low in non-lesion patients. He described Hunner's lesions as a well-defined entity, with characteristic cystoscopic and morphological findings and an excellent response to treatment in contrast with the non-lesion patients. Dr Nordling once again reiterated his suggestion that the term IC should henceforth be used for the lesion patients.

Tomohiro Ueda, MD from Kyoto then discussed cystoscopic diagnosis, looking at a possible mechanism of glomerulation and the narrow band imaging system (NBI) for IC, noting that bladder lesions are easily and clearly recognised by NBI. He emphasised that while "experts" can now detect lesions much more easily than ten years ago, the normal clinician has considerably more difficulty. Symptom-based diagnosis (BPS) is useful for maximising the ability to identify potential patients with this disease. However, he noted that in Japan and East Asia IC has been treated very much like overactive bladder. He concluded by saying that we have to demonstrate the pathology which can induce IC-like symptoms, such as bacterial cystitis, CIS and chemical cystitis. Furthermore, he continued, we need to provide an easy tool to detect hypersensitivity of the bladder and epithelial angiogenesis, such as the neurometer and NBI cystoscopy, so as to facilitate diagnosis of IC by the general urologist.

Magnus Fall, MD, from Sweden, then reviewed treatment of Hunner's lesions. Focusing on local treatment of lesions, Dr Fall explained that at his hospital in Sweden they first perform cystoscopy and bladder distension using spinal or general anaesthesia, distending the bladder at a superimposed pressure of 80 cm H2O. Digital obstruction is sometimes necessary to prevent leakage. Filling should be stopped when no further fluid enters. Rinse the bladder and then re-examine. Therapeutic distension should be ten minutes. He demonstrated with a video how to carry out complete resection (TUR) of the lesions. He noted that scarring and bladder contracture, with destruction of the contractile and distensible elements of the bladder wall, is part of the natural course of long-standing Hunner disease. With regard to whether post-TUR scarring influences bladder capacity, he reported that in 15 of their patients there was an increase in bladder capacity, 6 with permanent scarring; in 12 there was prominent scarring, 5 of those with diminished capacity; in a further 2 there was diminished capacity without scarring and a remaining case with no change. In an extended series of 103 resected patients, 92 experienced substantial improvement of bladder frequency as well as pain. The average alleviation of symptoms was 23 months. In 7 patients there was no pain relief and in 11 patients no improvement in frequency. Dr Fall felt that TUR was effective because it removed inflamed nerve endings, reduced aggregates of potent inflammatory mediators and eliminated epithelial mast cells. Other methods of local ablation include YAG-laser coagulation or fulguration. An alternative is sub-lesional or intramural injection. However, sometimes it is no longer possible to perform resection and surgery is necessary.

Discussion:
There was a lively discussion following this presentation about whether or not cystoplasty had any value, whether and when cystectomy should be performed and about what you can see before distension as opposed to post-distension.

SESSION VI: PATHOPHYSIOLOGY

There were some truly amazing scientists in this session who gave us every confidence that people are working very hard behind the scenes to find answers to the enigma of IC**. Lori Birder, PhD**, USA, began this session with a presentation on the urothelium and cell-cell interactions. The highly complex urothelium is multi-layered with several functions, one being a sensory function. It also has a very efficient barrier function which may become disrupted for a number of reasons, may become weak with less ability to repair itself. Can the urothelium be repaired? Possibilities include liposomes which may improve the barrier function. Studies are in progress in this field. Dr Birder suggested that the epithelium may 'amplify' signalling in pathology. In the urinary bladder, activation of nerves by epithelial ATP may contribute to bladder hyperactivity / pain, just as in the airways activation of nerves by epithelial ATP may contribute to airway hyperactivity (COPD and asthma). In addition, the corticotrophin-releasing factor (CRF) pathway plays an important role in mediating endocrine responses to stress in the pelvic viscera. This has been studied in detail in the gastrointestinal tract. Hyper-secretion of CRF occurs in many stress- and pain-related disorders and can alter motility and sensation – even resulting in hyperalgesia. CRF has theoretically been suggested as a therapeutic target in the treatment of OAB and IC/BPS. Changes in CRF-neurotransmission may play a significant role in chronic visceral pain syndromes. Dr Birder summarised by saying:

- Altered release of urothelial-mediators can activate underlying nerves, contributing to bladder instability, hyperactivity and altered sensations in a number of conditions.
- Non-neuronal cells can 'amplify' signalling, particularly in pathology.
- The diagnosis of chronic disorders is 'symptom-based', which wax/wane or change during disease progression, presenting many challenges to treatment and understanding mechanisms.
- Therapies that work on bladder sensory mechanisms, affecting the CNS and/or periphery, could be useful to decrease sensory urgency/pain.

Naoki Yoshimura, MD from Pittsburgh then discussed pathophysiology – bladder afferents, looking at urothelial-afferent interactions and afferent hyperexcitability in IC/BPS; chemical mediators – NGF; chemical mediators – cytokines and pelvic organ cross sensitization. Dr Yoshimura showed a chart of the basic proposed pathogenesis of IC/BPS: starting with a bladder insult -> damage to the epithelial layer -> urine substance leakage and urothelial dysfunction -> activation of C-fibers and release of substance P -> neurogenic inflammation with mast cell activation -> more injury. Regarding urothelium and afferent interactions, he reported that a concept has emerged that the urothelium can communicate with afferent nerves and that afferent/efferent nerves communicate with the urothelium via chemical messengers -> urothelial-afferent interactions -> activation of afferent pathways -> IC/BPS symptoms (pain, frequency)? Mukerji G 2006 wrote that increased TRPV1 expression in suburothelial nerves correlates to the pain score in IC/BPS and that the number of TRPM8-positive nerves was increased in IC/BPS bladders. Furthermore, mRNA levels of acid-sensing ion channels 2a and 3 are increased in IC/BPS bladders (Sanchez-Freire 2011). Treatment with intravesical alkalinized lidocaine (sodium channel blocker) shows sustained relief from symptoms in IC/BPS patients (*Nickel JC, 2009*). Chemical mediators inducing afferent sensitization are: nerve growth factor (NGF) and cytokine/chemokine. NGF (urothelium or muscle) is an important chemical mediator inducing sensory nerve sensitization, leading to afferent hyperexcitability (*Ochodnicky 2012*). Urine and serum NGF levels increase in IC/BPS patients (*Kuo 2012*). In 2011, Evans RJ found that treatment with NGF antibody (tanezumab) significantly reduced pain/urgency in IC/BPS. Concerning cytokines/chemokines, he reported that IL-6 levels are significantly greater in IC patients' urine than in controls and it could be used as a marker of IC. IL-8 level is lower in IC patients' bladder tissues than in those from normal volunteers. T-helper type 1-related chemokines/cytokines such as CXCR3 binding chemokines and TNF-α are increased in the bladders of patients with Hunner's lesion. Significant elevation of cytokines/chemokines such as IL-16, IL-18, MCP-3 and TRAIL are found in IC/BPS bladder tissues. Reductions in urine MCP-3 and TRAIL levels are correlated with symptom improvement after bladder hydrodistension in IC/BPS.

On the subject of pelvic organ cross-sensitization, he noted that this may play a role in the overlap with CPPS. Chronic colitis in rats induces urinary frequency. Bladder afferent fiber hyperexcitability and mast cell infiltration in the bladder. Acute colitis in rats sensitizes spinal neurons receiving input from the bladder and bladder sensory neurons. Pudendal nerve ligation injury in rats induces urinary frequency associated with increased NGF levels in the bladder. HCl injection into the gluteal muscle in rats (fibromyalgia model) induces urinary frequency and plantar hyperalgesia. It has been hypothesized that neural cross-talk mechanisms may underlie pelvic organ cross-sensitization. (*Malykhina 2007*).
He concluded by saying that:

- Urothelial afferent interactions and afferent hyperexcitability are involved in IC/BPS.
- Nerve growth factor plays an important role.
- Neurogenic inflammation with cytokine production plays an important role.
- Pelvic organ cross-sensitization contributes to bladder pain/overactivity.

David Klumpp, PhD, from Chicago, USA, followed with a presentation on host responses to bacteriuria. Talking about the effects of bacteria in the bladder, he said that while quite a lot is known about this in terms of Urinary Tract Infection (UTI), it is different to know what might contribute to the symptoms that take patients to the physicians. But in the field of microbial pathogenesis, the symptoms are often ignored. A few years ago, Klumpp and colleagues started to address this in mice by considering a urinary tract infection and asymptomatic bacteriuria. In both cases there are large bacterial loads of e-coli and comparable inflammatory infiltrate and yet the host response is very different: some have a pain response while some have no symptoms at all. They looked at two e-coli strains which have many differences. Since many IC patients have a history of UTIs, they looked at whether repeated installation of uropathogenic e-coli (UPEC) caused chronic pain. This was not the case but they did find that a UPEC mutant lacking O-antigen did lead to chronic pain after a urinary tract infection had cleared. They continued using different strains and all their findings demonstrate that transient infection with e-coli may result in chronic visceral pain with the hallmarks of neuropathic pain, also causing anxiety and depression, thereby raising the possibility of an infectious etiology of IC. He summarized with the following points:

- Pain response is determined a priori
- Chronic pain can be induced from a transient infection
- Pain phenotype is independent of inflammation
- Clinical implication seems to be if you are infected with the wrong bug + have the wrong genotype/epigenome, you may develop chronic pain
- ASB e-coli seem to show analgesic activity.

Masayuki Takeda, MD from Japan then looked at mechanosensitive ion channels in the lower urinary tract function, noting that the urothelium is not only a barrier, but also has some mechanosensory functions. As urine is stored in the bladder, mechanical stretch stimulates bladder afferents. These urinary bladder afferent sensory nerves consist of small diameter Aδ and C fibers running in the hypogastric and pelvic nerves. Neuroanatomical studies have revealed a complex neuronal network within the bladder wall. Dr Takeda emphasised that the exact mechanisms underlining mechanosensory transduction in bladder afferent terminals remain ambiguous. TRPV4, TRPA1, TRPV1 and TRPM8 are candidates for mechanosensor in the human urinary bladder. If ATP is the most important signal transmitter for urgency/pain, VNUT is a target molecule for novel treatment of OAB and IC/BPS. Piezo may be another target molecule for novel treatment of these bladder disorders.

Karl-Erik Andersson, MD, discussed bladder-brain-body interactions in IC/BPS, looking at afferent signal generation and transmission, brain processing of afferent signals, cross-talk between pelvic organs and pathways contributing to symptoms from the pelvic. He explained how afferent signals are generated in the pelvic organs and transmitted to the brain and then processed in the brain. Brain responses to bladder fillings are never normal in patients with bladder pain and/or urgency. The processing in the brain of afferent activity from the bladder and/or pelvic organs is translated into urgency, frequency and pain in IC/BPS patients and to gastrointestinal symptoms in patients with IBS. Pain pathways and the CRF axis may contribute to symptoms from the pelvis.

The final speaker in this scientifically complex session was **Hann-Chorng Kuo, MD**, from Hualien, Taiwan, talking about biomarkers for IC/BPS and asking why we need a biomarker for IC/BPS? Evidence indicates, he said that IC/BPS is a heterogeneous syndrome and that the two subtypes, the lesion type and non-lesion type, represent different disease entities. Patients with overactive bladder and increased bladder sensation often confuse the diagnosis of IC/BPS. There is a need for non-invasive markers for the differential diagnosis between IC/BPS and other bladder disorders. A biomarker much studied is antiproliferative factor (APF) which is a small, 8 amino acid sialoglycosylated peptide identified in the IC/BPS bladder. It causes suppression of bladder urothelial cell growth, increase of transcellular permeability, lowers the expression of intercellular junctional complex and reduces HB-EGF production from urothelial cells (*Keay S. 2008*)

Analysis of urine sensory proteins, inflammatory proteins and apoptotic protein in IC/BPS patients might provide valuable biomarkers in identifying IC patients from patients with frequency/urgency with or without bladder pain. Differentiation between IC/BPS and OAB is not an easy task, but potentially it might be possible to find some candidate proteins between these two bladder disorders. Proteomic study provides a way for analyzing heterogeneous subgroups in IC/BPS.

Somatization symptoms are common in IC/BPS patients, he said. Elevated serum cytokines and inflammatory proteins suggest IC/BPS bladders could be involved in some systemic diseases. Increased serum NGF and cytokine levels might decrease the sensory threshold (pain, frequency, urgency) in certain organs such as the urinary bladder. Dr Kuo suggested that we might use serum cytokines and inflammatory protein level to identify IC/BPS patients. These proteins are useful in monitoring therapeutic results.

He concluded by saying that several urinary proteins were found significantly changed in patients with IC/BPS, typically APF, HB-EGF, and EGF. Urinary and serum NGF and cytokines provide additional diagnostic values for patients with hypersensitive bladder suggestive of IC. We can use apoptotic protein analysis in urine. Proteomic analysis of IC urine may find a cluster of proteins for differential diagnosis among IC, OAB and hypersensitive bladder. Dr Kuo emphasised that a goal should be to be able to identify the disease in patients at the earliest possible stage so as to be able to help them more effectively.

SESSION VII POSTER PRESENTATIONS PATHOLOGY/BIOMARKER AND ANIMAL MODEL

POTENTIAL URINE AND SERUM BIOMARKERS FOR PATIENTS WITH BLADDER PAIN SYDROME/INTERSTITIAL CYSTITIS. Hann-Chorng, Taiwan.

EFFECTS OF ADDITIONAL URAPIDIL DSOING TO INTERSTITIAL CYSTITIS (IC) PATIENTS. Ryo Sato et al, Japan.

DECREASED EXPRESSION OF STEM CELL MARKER CD44V9 IN THE BASAL CELLS OF BLADDER EPITHELIUM IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME. Akira Furuta et al, Japan & USA.

DOWN REGULATION OF APOPTOTIC AND INFLAMMATORY PROTEINS ARE ASSOCIATED WITH IMPROVED CLINICAL CHARACTERISTICS OF PATIENTS WITH INTERSTITIAL CYSTITIS AFTER REPEATED INTRAVESICAL BOTULINUM TOXIN A INJECTIONS. Yuan-Hong Jiang et al, Taiwan

DIFFERENT EXPRESSIONS OF THE BLADDER INFLAMMATION, APOPTOSIS AND BARRIER PROTEINS IN PATIENTS WITH BLADDER OUTLET OBSTRUCTION, INTERSTITIAL CYSTITIS, SPINAL CORD INJURY, RECURRENT URINARY TRACT INFECTION AND KETAMINE CYSTITIS SUGGEST A SIMILAR PATHOPHYSIO. Wei-Chih Chen et al, Taiwan

PATHOLOGICAL MECHANISM OF THERAPEUTIC EFFECT OF BOTULINUM TOXIN A ON INTERSTITIAL CYSTITIS/ BLADDER PAIN SYNDROME. Yuan-Hong Jiang et al, Taiwan

INCREASED SERUM CYTOKINES AND CHEMOKINES LEVELS IN PATIENTS WITH INTERSTITIAL CYSTITIS / BLADDER PAIN SYNDROME SUGGEST SYSTEMIC CHRONIC INFLAMMATION IS INVOLVED IN PATHOGENESIS. Yuan-Hong Jiang et al, Taiwan

DECREASE OF URINARY NERVE GROWTH FACTOR BUT NOT BRAIN-DERIVED NEUROTRPOPHIC FACTOR IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME SUCCESSFULLY TREATED WITH HYALURONIC ACID. Yuan-Hong Jiang et al, Taiwan

INCREASED UROTHELIAL CELL APOPTOSIS AND CHRONIC INFLAMMATION MIGHT BE THE CAUSES OF RECURRENT URINARY TRACT INFECTION IN WOMEN. Jia-Fong Jhang et al, Taiwan

CYTOKINE RESPONSES IN BPS/IC TYPE 3C. Yr Logadottir et al, Sweden

EXPRESSION AND FUNCTION OF P2X3 AND NK1 RECEPTORS IN RAT URINARY BLADDER WITH CYCLOPHOSPHAMIDE-INDUCED CYSTITIS. Cui Ling Li et al, China

DNA MICROARRAY ANALYSIS OF GENES DIFFERENTIALLY EXPRESSED IN THE MOUSE BLADDER TREATED WITH CYCLOPHOSPHAMIDE.
Toshiki Homma et al, Japan

SESSION VIII: TREATMENT OF IC/BPS

Dr Karl-Erik Andersson began this session with an overview of pharmacology. He reported that in 2000 Rovner *et al* and the Interstitial Cystitis Data Base Study Group discovered that among 581 women with IC/BPS, a total of 183 different types of therapy were recorded! So he looked at the hypotheses for using the different types of therapy. A paper from 2012 by Giannantoni *et al* concluded that limited evidence exists for the few treatments for IC/BPS. The lack of definitive conclusions is due to the great heterogeneity in methodology, symptom assessment, duration of treatment and follow-up in both RCTs and non-RCTs. Looking briefly at possible etiology again, he noted: mucosal disease with defect in bladder cytoprotection, mast cells in the bladder, autoimmunity or occult infection which he would look at as a basis for drug treatment. Defining targets, he listed

- Bladder structures – urothelium, lamina propria (ICC, afferent nerves), detrusor;
- Systemic mechanisms – autoimmunity, occult infection;
- Pain

Dr Andersson felt that not everyone is using the correct bladder nomenclature and a big effort should be made to standardise this terminology.

The function of the urothelium is: barrier, exchange, secretion and signalling, he explained. The mucosa consists of the urothelium and lamina propria. The rationale for some of the treatment given is a defect in the top GAG layer which may affect the permeability of the bladder and affect the underlying nerves. Keay *et al* 2004 suggested that IC may be caused by an inhibition of normal bladder epithelial cell proliferation, resulting in a loss of epithelial barrier integrity with subsequent exposure of sensory nerve cells in the bladder wall to urinary constituents. The group of drugs that can be used for this includes PPS, Heparin, DMSO chondroitin sulphate, HA, lidocaine, etc. We need, he said, to look more closely at the role of the interstitial cells in IC patients. Therapeutic targets also include P2X receptors and TPRV1. He also looked at resiniferatoxin and felt that this should not be totally discarded but that its effectiveness remains unknown. Botulinum toxin has been shown to be more effective with repeated dosage (*Giannantoni et al 2008*), while Kuo showed in 2009 that intravesical injections of BoNT-A followed by hydrodistension (HD) produced significantly better clinical results than HD alone. Pinto *et a*l 2010 claimed that trigonal injection of BoNTA is a safe and effective treatment for refractory IC/BPS, although this has led to some controversy he said. Dr Andersson touched on Tanezumab, an NGF antagonist, where the trials have been discontinued due to side effects although the concept is particularly interesting. Several treatments have been tried in connection with mast cells (cimetidine and hydroxyzine), but not in larger trials. Regarding autoimmunity, a number of drugs have shown success in a few patients, indicating that autoimmunity must play a role in some patients. While no chronic infection has been found, studies are still in progress. Regarding pain, more needs to be done to learn exactly what pain is in BPS/IC, what is the difference between pain and discomfort, where do all the different types of pain and unpleasant sensation with IC/BPS come from. Great emphasis should be placed on alleviating pain.

The main aims of pharmacological treatment, he said, are to alleviate symptoms including pain, to influence pathogenic mechanisms and ideally to stop any progress of the disease. Summarising, he said that there are many potential pharmacological targets and there may need to be different drugs for different stages of the diseases. Combination therapy may be needed to achieve a substantial response. Some patients show a dramatic response to treatment, while others show no response at all. Whatever the case, IC/BPS patients should not be given treatments that put them at any risk.

He underlined that the problem with all treatment is that a) the etiology and pathogenesis of BPS/IC are unknown and b) there is no consensus on the definition and diagnosis of the disease, making it impossible to design scientifically based therapies.

Hikaru Tomoe, MD, PhD from Tokyo, looked specifically at oral treatment and hydrodistension. Starting with pentosan polysulfate sodium (PPS), she explained that it is hypothesised to work by providing a protective coating in the bladder. It has been shown that the duration of treatment appears to be more important than the level of dosage. There have been conflicting studies about its efficacy and value as an oral drug.
The tricyclic antidepressant amitriptyline is commonly used to treat IC/BPS patients. It has at least three pharmacological actions: it has central and peripheral anticholinergic action, it modifies pain transmission in the central nervous system by inhibiting serotonin and noradrenalin reuptake and inhibits mast cell activity by blocking histamine H1 receptor. While amitriptyline may be beneficial at $\geq$ 50 mg daily, side effects such as mouth dryness, weight and drowsiness are limiting factors. Therefore a starting dose of 10 mg is often suggested. Suplatast tosilate (IPD-1151T) is efficacious for allergic diseases. In mouse studies it has been shown to inhibit the release of histamine and tumour necrosis factor alpha. No significant adverse event has been seen. While a report from Japan in 2000 suggested increased bladder capacity and improved symptoms without serious side effects, no significant difference was found between IPD and placebo in a phase III study. While pregabalin is FDA approved for neuropathic pain, studies in IC/BPS patients are lacking. Corticosteroids may be indicated for lesion IC or IC related to autoimmune diseases.
On hydrodistension, Dr Tomoe reported that hydrodistension is the most common treatment for IC/BPS. There has been no randomised comparative study. In Japan hydrodistension is a first choice treatment for IC/BPS. The efficacy rate is believed to be around 50%, but the effect only persisted for about 6 months. Its mechanism of action is unknown but it may in rare cases cause complications such as bladder rupture.

Arndt van Ophoven, MD, PhD, from Germany then discussed other treatments, including a conservative approach with avoidance of symptom triggers the patient may have identified such as food and drink (comestibles) and smoking, noting that genetic factors may play a contributory role. Myofascial physiotherapy has been shown to have a beneficial effect. Looking at intravesical treatment, he discussed the novel lidocaine-releasing intravesical device (LiRIS) currently undergoing trials and which looks promising and appears to show mucosal healing.

Michael Chancellor, MD from the USA then discussed novel therapies:
Novel therapy with intravesical liposome in clinical trials began some ten years ago when everyone was excited about capsaicin, he said. Liposomes were used as the vehicle, but to their surprise the vehicle worked just as well. The concept is that if there is a defect in the urothelium itself, the liposome can perhaps coat and integrate and restore the damaged urothelium. Some of this research has been brought under the company Lipella for pioneering intravesical therapy. It mission is to be the leader in the development of new intravesical therapies to treat urinary bladder diseases. This is an experienced team with a pilot scale manufacturing centre, an exclusive license to two issued US patents, with additional applications filed in the US and internationally.
Lipella current disease targets include:

- LP-08 (Liposome) for IC/BPS
- LP-09 (Lipo-Botulinum toxin) for OAB
- LP-10 (Lipo-tacrolimus) for hemorrhagic+radiation cystitis.
- Liposome is a platform for drug delivery with high potential.

Looking at Nerve Growth Factor, he said that it seems clear that this plays an important role, but how can we target it without severe safety issues as occurred with systemic administration of monoclonal human NGF antibodies (tanezumab) which encountered safety concerns such as paresthesia, hypoesthesia and arthralgia. How can it only be blocked in the bladder? Preliminary studies have indicated that liposomes restrict the action of drugs instilled in the bladder and avoid systemic side effects.

<u>Hyperpolarisation-activated Cyclic Nucleotide-gated ion channel 2</u>
Dr Chancellor discussed a potential new target with the HCN2 gene which seems to play a central role in inflammatory and neuropathic pain. According to Emery et al, 2012, Deletion of the HCN2 isoform from nociceptive neurons abolishes heat-evoked inflammatory pain and all aspects of neuropathic pain, but acute pain sensation is unaffected. This work shows that inflammatory and neuropathic pain has much in common, and suggests that selective blockers of HCN2 may have value as analgesics in the treatment of pain.

He concluded by saying that treatment in the future will need to be personalised to the individual patient.

Nagendra Mishra, MD from India rounded off the session by looking at the possibilities of intravesical tacrolimus in IC/BPS. Tacrolimus is an immunosuppressant used in kidney and liver transplant. Its mechanism of action is similar to cyclosporine. Its most common complication is drug-induced diabetes. Rationale: Tacrolimus is used in rheumatoid arthritis and atopic dermatitis. Cyclosporine is used in IC/BPS and has been found to be effective but is given orally and has a lot of side effects. With intravesical delivery, the drug would be delivered at the site of action. Tacrolimus is not soluble in water, but it is soluble in DMSO which is also commonly used intravesically for IC/BPS. Dr Mishra's hypothesis is that intravesical tacrolimus in the dose of 0.08-0.1 mg per kg body weight will be able to control the symptoms, while the side effect profile will be negligible when instilled intravesically. While it is still too early to comment about results of preliminary studies in India, it looks quite encouraging, he said, and there have been no side effects which can be attributed to tacrolimus.

Discussion
In the discussion that followed this session, an important question was raised by Dr Homma on how to effectively and objectively evaluate the efficacy of treatment. Patient self-assessment may be useful for clinical use per individual patient, but some better standardised way is needed in research.

SATURDAY, 23 MARCH

SESSION IX: SPECIAL SOCIETY OF INTERSTITIAL CYSTITIS JAPAN (SICJ) LECTURE BY PROFESSOR YUKIO HOMMA: HYPERSENSITIVE BLADDER: STATE OF THE ART – A SOLUTION FOR CONFUSED TERMINOLOGY AND A SOLUTION FOR LIMITED INTEREST OR IGNORANCE.

Referring to the confusion in nomenclature, Dr Homma noted that even at this meeting of experts, speakers were all using different terminology!
There is he said:

- Confusion regarding symptom, syndrome, condition, disease…
- Confusion regarding pain, discomfort, urgency, unpleasant sensation…
- Confusion for both physicians and patients…

Many of the definitions for PBS or BPS refer only to symptoms and exclusion of confusable diseases and no objective findings. It is unclear whether we are talking about a collection of symptoms, a syndrome or a disease. It is confusing for researchers, for patients and for the general urologist who cannot understand what is meant and consequently prefers to ignore its existence. In other words, an ambiguous definition and inaccurate use of terminology leads to confusion in clinical practice and research.
Dr Homma explained that a problem with either PBS or BPS (and all their combinations) is that the terms contain the word 'pain', thereby conveying the impression that pain is essential, whereas many patients in fact have discomfort, irritation with very little urine or pressure which they themselves do not identify as being pain. What is the difference between pain and discomfort, what is an unpleasant sensation, he asked? The term pain does not adequately describe the symptoms and may be too restrictive. The IASP definition of pain is very much a researcher's definition and not a patient-centred definition and it is unrealistic for the general physician and patients in a clinical setting to consider discomfort as being pain. If you ask patients, they will say that discomfort or irritation is not pain. Pain is beyond discomfort. Patients often also say that they no longer have the normal sensation of needing to void. It has changed. They have an incessant need to void due to discomfort. Their complaints are suggestive of visceral hypersensitivity of the bladder.
So the East Asian countries felt that a new symptom term was needed that encompasses pain in the broadest sense without using the term pain and that hypersensitivity would be better. He noted here that many speakers had already pointed out that the urothelium is a very sophisticated sensory tissue.
The term hypersensitivity has its origins in an ICS standardisation document where it meant increased bladder sensation and an early and persistent need to void.

So they finally opted for the term hypersensitive bladder (HSB) which is a bladder condition with HSB* symptoms in the absence of obvious diseases and keeping IC as a disease name.

* increased bladder sensation, usually associated with frequency and urgency, with or without bladder pain. Hypersensitive bladder can be seen as a counter-concept of overactive bladder.

In East Asia, the term Interstitial cystitis is a specific diagnosis defined by 3 conditions:

1) Hypersensitive bladder symptoms
2) Bladder pathology
3) No other obvious diseases.

In other words, IC denotes a disease with HSB symptoms AND bladder pathology.

Comment:
HSB could also cover that group of patients left in a grey area between IC/BPS and OAB which have largely been ignored until now. Where patients are concerned, HSB is certainly a very patient-friendly concept since it ensures that no-one is excluded. What was interesting was to see that many of the international delegates seemed to think that this was a cultural problem relating to Japan – that Japanese patients don't speak of pain – whereas the patient organisations around the world are aware that this is a worldwide phenomenon and that patients who don't interpret their discomfort as being pain and consequently say they have no pain are either sent home with no diagnosis or wrongly diagnosed.

SESSION X: FUTURE DIRECTIONS

Christopher Payne, MD from the USA opened this session on future directions by looking at some of the key issues concerning the future and said that, in terms of diagnosis, we are going to need to go from "lumping" all the patients together to "splitting" them into groups. He felt that mistakes had been made a long time ago, but now classic interstitial cystitis (Hunner's lesion) must be split off from bladder pain syndrome. The lesion patients are unquestionably a different patient population, he said. There should be a new focus on identifying this subgroup since there is an especially good prognosis and they can really be helped. And it is essential to split them off for research purposes, since we have something we can measure, something we can biopsy and study. The past lumping together has hindered our research very badly.
The patients with bladder pain syndrome also need to be split out into groups and the buzzword is going to be phenotyping. For example, phenotyping by identifying the source of the pain: is it from the bladder, the pelvic floor or elsewhere. Another example: phenotyping based on localised versus systemic pain. Other phenotypes that could be identified include: glomerulations versus none, patients with systemic pain syndromes, patients with autoimmune diseases, patients with multiple allergies, patients with predominant pain and minor LUTS and the opposite: predominant LUTS and little or no pain; and children and men. He added that large cooperative groups will be needed to study such subpopulations and this will be the way forward.

On biomarkers: maybe by researching BPS phenotypes, we will find biomarkers for specific subtypes. He felt that insufficient attention is currently being paid to physical examination of the patient and identifying where the pain is coming from.

In the field of treatment, there needs to be recognition/exploitation of pelvic floor dysfunction (PFD), he said, and we are likely to see an explosion of new treatment options. He felt that in the future there was likely to be a completely different approach focused on aiming for complete remission.

On the topic of physical therapy, he felt that this was being greatly under-utilized at the present time. This can be a combination of using myofascial triggerpoint release and paradoxical relaxation rather than physical therapy alone. He explained that at Stanford their problem is how to deliver this treatment more effectively as it is far too unavailable and expensive at the present time. They need to learn how to best select patients and understand what works. At Stanford, this is home-based therapy, directed by a urologist. The patients learn techniques for external trigger points. There is now a new pelvic "wand" to reach internal trigger points. The patients can use an MP3 player to follow weekly instructions on therapy, with paradoxical relaxation.

There are many new targets for treatment including the whole of the urothelium, receptors and transmitters, as well as the central nervous system. There are also new, greatly improved drug delivery systems which have already been discussed at the meeting (e.g. liposomes). This is specifically for patients whose pain is clearly coming from inside the bladder and he stressed that we really need to learn how to select these patients better.
On the subject of approach, he felt that a new approach is needed to the patients by the physician, be less negative and more positive, focusing on getting well and ultimately achieving a complete remission.

Magnus Fall, MD then addressed the delegates on where Europe is going, reporting that the last decade has seen a paradigm shift in Europe. This is due to the work of the ICS Standardisation Committee, ESSIC and the EAU Guidelines project. He emphasised that the better you describe a disease, the better you understand it. He also felt that they had been going in the wrong direction for year but have now taken a turn in the right direction. The EAU chronic pelvic pain guidelines committee was established in January 2002 and the first version was 2003. Several versions of the guidelines have been published since then, the most recent being the third full CPP text in 2012. It is quite clear, he said, that we are dealing with multi-symptom disorders. Evidence is accumulating of central nervous system changes and sensory changes in many of these patients. There are associations with other conditions, in other words multisystem problems. We therefore place emphasis on the multidisciplinary approach, he said. There is a complexity of pain mechanisms, making them difficult to grasp. You have to accept the concept of pain as a disease process in its own right. Dr Fall also stressed that phenotyping is absolutely necessary to go forward in the future.

Alex Lin, MD from Taiwan looked at the Asian view, based on the views of a number of IC/BPS experts in Taiwan. They believe it is now vital to develop a consensus definition and diagnostic criteria for IC/BPS and to be able to detect and treat patients at an early stage. He said that, although there was still a gap between east and west, he felt that the gap was narrowing. They also feel it is important to classify patients clinically according to phenotypes. This can be done, he said, according to the symptoms, using hypersensitive bladder with/without pain, and according to with/without comorbidities. Although urodynamics is not a diagnostic criteria, it is possible that different types of patients may have different urodynamic findings. This tool may also be used to phenotype the patients. We have a lot of biomarkers, he said, and we can use different biomarkers to identify patients for specific treatment. The genetics study from Japan also points us in a good direction for future classification. He emphasised that in Asia the biggest priority is to develop a treatment to help their patients. One of the directions they wish to take with regard to intravesical treatment is botulinum toxin injections, either on demand or scheduled repeated injections, identifying predictors for a positive response because this treatment is invasive and costs money so no-one wants to be giving treatment to patients where it is not going to work. Instillation of liposomes or a liposome-related regimen is another. This looks like a very promising treatment for the future. Novel oral medication may include adrenergic beta blockers, or Fatty Acid Amide Hydrolase (FAAH) inhibitors as possible future developments.
Another important aspect in Asia and a challenging topic for research is how to differentiate male patients with IC/BPS from CPPS. Could male IC/BPS and CPPS patients have the same disorder originating from chronic inflammation?
A big public health problem in Asia is ketamine-related cystitis, particularly in Taiwan and Hong Kong where there are a lot of patients, usually young people. Research into its pathophysiology and treatment will certainly add to our knowledge of IC/BPS, said Dr Lin.
Looking at uropsychology in IC/BPS, he said that IC/BPS symptoms are positively correlated with the level of anxiety and depression. Establishing a psychological profile is an important aspect of caring for the patients. They believe that it is very important to develop a collaborative holistic care model. IC/BPS is a multi-factorial disorder, affecting many aspects of the patient's life and requiring multidisciplinary care. However, there are generally limited resources available for these patients in Asia and it is necessary to campaign to gain the attention of the healthcare system to support development of a collaborative holistic care model which may be delivered in person, in clinics or though modern communications such as internet or smart phones.

The next topic was chronic pelvic pain and its sexual implication by **Kristene Whitmore, MD**, top expert in this field. Addressing chronic pelvic pain syndromes, she first looked at the term syndrome. What is a syndrome? It

comprises symptoms and signs that collectively indicate a disease, dysfunction or disorder. What is a symptom? Symptoms are how a patient personally experiences a disorder or dysfunction and is always subjective, in other words the history. What is a sign? Signs are what your healthcare provider can view as a deviation from normal function or structure and are always objective, the physical examination. CPP syndromes include: lower urinary tract pain, male genital pain, female genital pain, gastrointestinal pain, musculoskeletal pain, neuropathic pain, psychological overlay, sexual pain, sexual disorders, related conditions outside the pelvic. Lower urinary tract pain consists of bladder and urethral pain or discomfort or unpleasant sensation. Dr Whitmore emphasised a multidisciplinary approach. Sexual dysfunction is one of the most common complaints of both male and female patients, including problems with desire, arousal, orgasm and satisfaction. She offered a variety of treatment approaches.

Perhaps the most movingly patient-centred presentation of this conference was the presentation by **Ming-Huei Lee, MD** of Taiwan on patient communication including the sexual implication of IC and why holistic management is important for care of IC patients. He explained some of the background to guidelines used in Taiwan, reporting that cystoscopy has to be performed for approval to be given for many treatments. The aim of treatment is to provide the patients with an acceptable quality of life and support. Patient-centred healthcare means understanding and respecting the patient's value, preference and expressed needs. When the patients go to the doctor, they are distressed, they want to know what the problem is, they want to know if they have cancer, and want information. They are experiencing stress in their relationship, sexual disability, job performance and social activity. Emotionally they are often depressed, afraid about their future and frustrated by failure of treatment.
What the patient is seeking is a cure for the disease, while the physician can only offer care (for symptoms, sexuality and quality of life). The patients in Taiwan – like in other countries – go hospital shopping, hoping to find a cure. However, by giving the patient assurance and support, we can gain the trust of the patient, he said.
The first step in management of the disease begins with empathy and communication with the patient. And this communication must include sexual aspects. However, while there are diverse treatments available, no single one is specific. An additional problem is formed by comorbidities and the fact that different pathophysiology may require different types of treatment. Multidisciplinary treatment is best for these patients. At his hospital, they assemble many different specialists, including holistic, traditional Chinese medicine and acupuncturists, to discuss the cystoscopic findings and then try to explain to the patient what treatments are possible and to obtain their agreement to undergo treatment. He said that they also have many good international connections in Taiwan for research and they make sure that the patients know that research is being done for them so as to give them confidence.
The long-term physical distress suffered by these patients could lead to a psychological burden, impaired interpersonal and occupational performance as well as decreased quality of life. Social aspects are particularly important, he said, because society is not very friendly to IC patients. So you need to establish a social mantle to help the patient and this is where the Taiwan Interstitial Cystitis Association (TICA) plays a valuable role. Their IC integration team organises activities on a regular basis with TICA and public relations campaigns such as news reports in newspapers and magazines and press conferences. The TICA support system provides newsletters, a quarterly magazine, a website, outdoor recreational activities, small gatherings and annual conference activities. They have also set up Taiwan's first IC e-health remote healthcare system. And in 2011 their hospital Bio-Psycho-Social Model Holistic Health Care Team received a special Symbol of National Quality 2011Award. He ended by saying that while they wish they could cure IC/BPS, they hope they can at least conquer IC/BPS.

Discussion
In the discussion following this session and with reference to guideline committees, it was noted that there is very little patient participation in guideline, taxonomy, classification and ICD-11 committees and task forces. Patient representatives are often not being invited to participate in any of these committees, despite the fact that they have considerable expertise and knowledge. Patient organisations have contact with hundreds and often thousands of patients through their helplines and this given them a wide view of the whole spectrum of patients which professionals/researchers often don't have. The patient representatives can therefore provide an extra dimension, pointing out aspects that may have been overlooked and thereby provide a valuable contribution to such committees.

It was pointed out that the MAPP project is concerned with some phenotyping and D. Klumpp asked whether, bearing in mind what had been said about lesions, was it an important omission on the part of the MAPP phenotyping that cystoscopy is not a component of that? J. Nordling felt that it was indeed a problem since this is a subgroup with important cystoscopic findings and perhaps this should be included in Phase II. M. Fall felt it was important to register as many objective findings as possible, even if we don't know what they mean right now, otherwise the data is not going to be complete or provide a comprehensive picture in the future.

SESSION XI – TAKE HOME MESSAGES

Dr Jorgen Nordling kicked off this session, saying that during this meeting we had heard about definition, diagnosis, pathophysiology and treatment. We had also heard much about basic science, including

- Urothelium and cell interaction
- Bladder afferents
- Ion channels
- Bacterial provocation of chronic pain
- Biomarkers

There is a huge amount of basic science knowledge available. But in the clinic, he said, we are still left with disabled patients and very few good options for treatments. So we have to look carefully at how we get this basic science knowledge out to the clinics.
A first step in the right direction would be if we could all use the same terminology and definitions, and also by subclassification and phenotyping. There are many possibilities for phenotypes, for example pain/discomfort, food sensitivity, pelvic floor tenderness, localisation of pain, autoimmune diseases, associated disorders, sexual pain m/f, ejaculation pain, urinary symptoms, pain descriptors, functional somatic syndromes and biomarkers.

Furthermore, he emphasised that it has been very difficult in the past – and still is – to know exactly what the patient material was in studies. It is essential for researchers to describe very clearly IN DETAIL the patient material in their studies in both their papers and the abstract. And Dr Nordling said that this would be his most important take-home message.

Dr Philip Hanno then looked at name and definition harmonisation and the problems that are still not fully resolved. He underlined what Dr Nordling said that it is critical for authors of papers to state exactly what patients they are talking about and not rely entirely on the different terms. One problem in the USA is that the FDA is still clinging to old NIDDK definitions. What data would encourage them to change to the new guidelines around the world?
Outstanding issues include asking why the prevalence of this disorder appeared to increase from Oravisto's 18/100,000 with a 10:1 female to male ratio to the RAND/NIDDK estimate of 2700/100,000 females and 1900/100,000 males? Is this related to better definition, better methodology? Are we diagnosing people on epidemiology studies that really don't need diagnosis or treatment? Have we been or will we be able to harmonise Asian and North American/European nomenclature and definitions? Can we define hypersensitive bladder as an independent entity distinguishable from BPS and OAB? Should the term interstitial cystitis be redefined and used for Hunner's lesion and make this a separate group? How much more data would we need to be able to do this?

Robert Moldwin, MD then summed up treatment. If you want to have the best treatment outcome for your patient, he said, you have to begin with the correct diagnosis. Many of the patients have multiple co-morbid conditions, often also with pelvic floor dysfunction, that have to be taken into consideration. However, if therapy is not effective, consider other diagnoses altogether or co-existing disorders. Treatment should start with conservative management and move towards aggressive. However, this has to be done on an individualised basis. A patient coming in with severe symptoms and Hunner's lesions is not likely to benefit from simply dietary changes. We should always weigh up the risk versus the benefit. Self help is very important and includes patient support groups, bladder retraining, behaviour modification, physical therapy/yoga, herbal therapy, biofeed/electrical stimulation, acupuncture, warm baths/heating pads, dietary modification by starting with a bland diet and gradually add items of food or drink to see why might elicit symptoms.

Urinary anaesthetics are used frequently but discussed rarely, including phenazopyridine (Pyridium) and methylene blue. He emphasised that IC patients can get recurrent infections just like any other person in the population and this should be treated with antibiotics.

Dr Naoki Yoshimura, USA, the last speaker, not only of the session but also of the conference, summed up basic research by first asking: why is basic research needed? He explained that this is because the etiology of IC/BPS/HSB is still not know but is likely to be multifactorial. We need to understand the biochemical, physiological and pathophysiological mechanisms, either validated or postulated, of the disease. A better understanding of the pathophysiology will lead to better treatment. Basic research using animal models permits a controlled analysis of some aspects of this chronic syndrome. Animal models allow us to perform the study in controlled conditions (e.g. duration and/or severity of insults) and to utilise invasive experimental methods that cannot be used in patients. However no animal model represents all aspects of the disease and it is difficult to develop an animal model that fits all aspects of disease conditions. We need to understand which and how proposed mechanisms are reproduced in each of the animal models. When starting research we need clinical evidence, a clear hypothesis on which to build, then we find the animal models and follow it up with clinical validation. Feline idiopathic cystitis (FIC) is a naturally occurring model and the closest model to human IC/BPS, but has limited availability. He reviewed research on urothelial pathology, explaining that following some initial insult on the bladder, something clearly goes wrong in IC/BPS patients. Basic researchers have to explore every channel, looking at epithelial layer damage, urine substance leak and urothelial dysfunction, activation of C-fibers and release of substance P, neurogenic inflammation with mast cell activation, leading to more injury. Additional problems the basic scientists look at include interaction with other organs, organ cross-talk, pain behaviour and assessment; also stress reaction since stress can aggravate symptoms in patients and changes in the brain and nervous system. With phenotyping, they have to differentiate IC/BPS from other diseases and look for differentiation within the disease itself, and interaction with other disease conditions. Based on disease phenotyping, it is hoped then to find new targets for treatment.

Yukio Homma, MD then said a few words, expressing hope that the confusion with definitions and terminology could be resolved and noted that Hunner's lesion now appears to be a quite separate disease. And he too stressed that it should be stated clearly in be scientific papers whether the patients in a study have lesions or not. Regarding treatment, he said that a current big problem is that treatment that works in one patient does not work in another who nevertheless appears to have a similar condition.

Dr Hanno then thanked Dr Ueda for organising the conference and Dr Ueda closed the meeting, saying that they hoped to organise an ICICJ meeting every four years.

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