CHAPTER 2

INTERSTITIAL CYSTITIS IN THE NETHERLANDS: PREVALENCE, DIAGNOSTIC CRITERIA AND THERAPEUTIC PREFERENCES

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Abstract.

Purpose. To determine the prevalence of interstitial cystitis in The Netherlands and to analyse the most common diagnostic and therapeutic approaches among Dutch urologists.

Materials and Methods. A questionnaire was filled in by urologists and analysed with the help of a statistical computer program.

Results. The prevalence of interstitial cystitis was calculated between 8 to 16 per 100,000 female adults. Pathology of bladder biopsies and mast cells were the main diagnostic criteria. DMSO instillations, bladder hydrodistension and surgery were the most frequent applied therapies.

Conclusions. The prevalence of interstitial cystitis in the Netherlands is in line with other reports from Europe, but low compared to the USA. The importance of pathology and mast cells in diagnosis and less awareness might contribute to this difference.
INTRODUCTION
In 1915, Hunner (Boston) described "a rare type of bladder ulcer", that is "areas of hyperaemia which, on being touched with a dry cotton pledget bleed and first show their character as ulcers"¹. The symptoms in the (female) patients were urge, frequency and suprapubic pain. Patient age was 20 to 40 years. This complex of symptoms and characteristic cystoscopic findings is currently recognised as interstitial cystitis and the study by Hunner has become the most frequently cited among articles on interstitial cystitis. Despite the long standing recognition of interstitial cystitis, there are still no definite answers to vital issues such as its etiology, prevalence, diagnostic definition and therapy. Patient advocate groups in the United States have generated recognition, and there has been an exponential growth in clinical and basic research since the 1980s. In contrast to the situation in the United States, epidemiological data and research on interstitial cystitis are severely lacking in Europe. However, interstitial cystitis is a major health problem and is one of the most frequent benign indications for cystectomy, and 50% of the patients are declared unfit to work². It will be necessary to identify and group interstitial cystitis patients for a greater insight into the condition and to develop effective management regimens.

A population-based study to determine the prevalence of interstitial cystitis would require a large sample of patients because of the low frequency of interstitial cystitis in the general population. A patient-based study is not possible because of the absence of an organised registry for interstitial cystitis or a patient association. However, it can be expected that with time all interstitial cystitis patients will consult a urologist because of the severity of the complaints. Therefore, we decided to conduct a survey among all urologists in The Netherlands, including a questionnaire, and registration of the most common diagnostic and therapeutic approaches.

METHODS
A questionnaire was developed in cooperation with the department of epidemiology of our university. The face-validity of the questionnaire was evaluated by sending it to all staff members at the urology department and their comments were used to compose the final version. The questionnaire was then sent to all Dutch urologists. The majority of the questions were precoded and the survey was anonymous.

The questionnaire had three parts: 1) epidemiological section- urologists were questioned for the average number of patients seen per year with chronic micturation disorders, and the number, average age and gender of interstitial cystitis patients treated, with additional information was
obtained on the disease history and presenting symptoms in interstitial cystitis patients, 2) diagnostic section- questions were asked regarding diagnostic investigations and diagnostic criteria for interstitial cystitis patients, and 3) therapy section- urologists were questioned on the most common therapy modalities, and were asked to indicate the first, second and third choices. If surgery was performed, they indicated the preferred surgical technique. All urologists indicated which regional cancer registration center applied to their hospital. In this manner, potential regional differences in prevalence rates, and diagnostic and therapeutic practices could be detected. In addition, all urologists were asked to provide an estimate of the annual number of new cases of prostate cancer and bladder cancer seen in practice. The number of cancer cases in each region could be calculated from these data and compared to the official statistics given by the cancer registry, which provided an indication of the urologist reliability in estimating the prevalence of interstitial cystitis in The Netherlands.

RESULTS

Questionnaires were sent to 235 urologists and 153 were returned, for a response rate of 65%. All data were used to estimate the prevalence of interstitial cystitis. No cases of interstitial cystitis were reported on 21 questionnaires, which along with 10 incomplete questionnaires, were excluded from further analysis. The remaining 122 questionnaires were used to analyze additional epidemiological, diagnostic and therapeutic data using a statistical computer program.

A total of 97 urologists treated 1 to 5, 20 treated 5 to 10 and 5 treated 10 to 15 interstitial cystitis patients per year. The calculated prevalence of interstitial cystitis was 8 to 16 cases per 100,000 females. Extrapolation to the general population produced an expected group of 400 to 1,300 interstitial cystitis patients. Interstitial cystitis comprised 10% of all chronic functional micturition disorders. The correlation between the urologist-based estimates of (new) prostate and bladder cancer cases and the cancer registry rates were fairly good (0.87 for bladder cancer and 0.64 for prostate cancer).

Only 48% of the respondents reported interstitial cystitis in male patients, with a male-to-female ratio of less than 1:10. Analysis showed that 93% of interstitial cystitis patients were 20 to 60 years old and 91% had a disease history of 1 to 5 years. The most frequently reported symptoms of interstitial cystitis were frequency in 87% of the patients, pain relieved by emptying the bladder in 61%, suprapubic pain in 61% and urge in 57%. When interstitial cystitis was suspected the main investigations were urine culture or urine cytology studies (more than 90%) followed by cystosco-
py with or without biopsies and cystometrograms. Ultrasound and x-ray examinations comprised less than 40% of the studies.

Table 1.

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<tr>
<th>DIAGNOSTIC CRITERIA FOR INTERSTITIAL CYSTITIS</th>
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<tr>
<td>PATHOLOGY OF BLADDER BIOPSIES</td>
<td>91%</td>
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<tr>
<td>HISTORY AND VOIDING LOG</td>
<td>83%</td>
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<tr>
<td>MAST CELLS IN BLADDER BIOPSIES</td>
<td>79%</td>
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<tr>
<td>CYSTOSCOPY UNDER ANAESTHESIA</td>
<td>63%</td>
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<td>CYSTOSCOPY</td>
<td>56%</td>
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<tr>
<td>URODYNAMIC INVESTIGATION</td>
<td>55%</td>
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<tr>
<td>NIH CRITERIA United States</td>
<td>26%</td>
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Table 1 shows the various criteria used to diagnose interstitial cystitis. Pathology on bladder biopsies was reported most frequently (91%) and slightly more often than was a typical disease history (83%). The presence of mast cells in bladder biopsies was used as a diagnostic criterion by 79% of the urologists, while only 26% applied the United States National Institutes of Health (NIH) criteria. In most cases, a combination of three or more criteria had to be fulfilled to establish a definite diagnosis of interstitial cystitis: 9 urologists (7%) used two criteria and four (3%) used only 1 criterion (mast cells in 2 instances, histology in 1 and cystoscopy with the patient under anesthesia in 1).

A wide variety of therapies were applied (table 2). Dimethyl sulfoxide instillations and prolonged static bladder hydrodistension (Helmstein method) were used by 80% of the urologists. Miscellaneous therapies consisted mainly of non-steroidal anti-inflammatory drugs, anti-cholinergics and prolonged antibiotic courses. If conservative treatment failed, 88% of the urologists considered surgery as optional therapy. However, the number of interstitial cystitis patients finally undergoing surgery varied from 0% (18% of urologists) to more than 50% (9% of urologists). Augmentation
ileo-cystoplasty (39%), subtotal cystectomy with entero-cystoplasty (34%), total cystectomy with urinary diversion (23%) and urinary diversion only (4%) were the preferred surgical techniques. A few urologists (11%) performed surgery as the first or second treatment option.

Table 2.

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<tr>
<th>TREATMENT MODALITIES USED FOR INTERSTITIAL CYSTITIS</th>
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<tr>
<td>urologist - based questionnaire, The Netherlands</td>
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<td></td>
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<tr>
<td>D.M.S.O. BLADDER INSTILLATIONS</td>
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<tr>
<td>HYDRODISTENSION (HELMSTEIN)</td>
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<td>PENTOSANPOLYSULFATE</td>
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<td>AMITRYPTILINE</td>
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<td>CORTICOSTEROIDS</td>
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<td>ANTIHYPHLOGISTIC INJECTIONS</td>
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<td>SILVER NITRATE INSTILLATIONS</td>
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<td>CATHETER</td>
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<td>MISCELLANEOUS</td>
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DISCUSSION
From a urologist-based questionnaire the prevalence of interstitial cystitis in the Netherlands was estimated to be 8 to 16 cases per 100,000 females. Extrapolated to the entire population yielded approximately 400 to 1,300 (symptomatic) interstitial cystitis cases. However, the reported cases were estimates. To assess the accuracy of the urologist’s estimates they were also asked to estimate the number of (new) prostate and bladder cancer cases in 1992. The actual number of prostate cancer and bladder cancer cases (incidence figures for 1992) were provided by the regional cancer registries. Estimated numbers and registered numbers correlated fairly well (0.87 for bladder cancer and 0.64 for prostate cancer). These findings support the reliability of the calculated prevalence in this study. However, the interstitial cystitis estimates mainly reflect the number of interstitial cystitis
patients who consulted a urologist in 1993. The total number of interstitial cystitis patients would be much larger if those who had undergone bladder substitution therapy in the past and those who withdrew from treatment were included. Therefore, the calculated prevalence is probably a conservative estimate.

Studies on interstitial cystitis prevalence are rare. The most frequently cited was a regional population-based study performed in Finland in 1975, which reported a prevalence of interstitial cystitis of 18.1 per 100,000 women\(^3\). A similar figure (patient-based estimate) was reported at a third line referral (university) hospital in Sweden\(^4\). Prevalence figures for the United States are mainly based on the study by Held et al (30 per 100,000 male and female patients)\(^2\), which is almost double the prevalence rates reported in Europe \(^3,4\). A recent study in the United States claimed a prevalence that was 10 times higher than the aforementioned European figure \(^5\). How should one interpret the lower European prevalence estimates compared to those in the United States? There are 3 possible explanations: 1) the study methodologies may have differed, 2) there may be a genuine difference in prevalence between Europe and the United States and 3) different definitions may have been used. Explanation 1 refers to differences in methodology. Population-based questionnaire studies, as used in the United States, may easily have included patients with symptoms that resembled interstitial cystitis but who were not diagnosed as having interstitial cystitis. However, also in the urologist-based study by Held et al, the prevalence rate in the United States was twice as high as the European figures\(^4\). Explanation 2 refers to a genuine difference in prevalence between Europe and the United States. However, to date no geographical factor has been reported to influence interstitial cystitis and the preference among the white interstitial cystitis patients should cause rather an opposite genuine difference. Explanation 3 was a possible difference in the definitions of interstitial cystitis. In the United States clinical inclusion and exclusion criteria to define the diagnosis of interstitial cystitis were formulated in 1988\(^6,7\) and are presently being used by the majority of urologists. Our study revealed that general and specific (mast cells) pathological features of bladder biopsies are the most important diagnostic criteria being used by Dutch urologists. The ratio of mast cells as a diagnostic marker for interstitial cystitis has been criticized in the past\(^8,9\). However, in our study almost 80% of Dutch urologists used mast cells as a diagnostic criterion. If too much weight is placed on the outcome of a single investigation other positive findings may be overruled, causing the under-diagnosis of interstitial cystitis and, therefore, explaining the difference in prevalence between The Netherlands (Europe) and the United States. Explanation 3 probably is the most convincing. In addition, one may speculate about a difference in
awareness concerning the diagnosis of interstitial cystitis. In the United States, an active Interstitial Cystitis Association exists for patients and physicians, which association encourages awareness, information, education and research on interstitial cystitis. It forms a tight network of support for patients and assists physicians once the diagnosis of interstitial cystitis has been established. These conditions are virtually nonexistent in Europe. Less awareness and, in addition, a bleak prognostic perspective once the diagnosis has been made may cause a vicious circle resulting in a restrictive policy for diagnosis of interstitial cystitis. As reported in our questionnaire, the symptoms presented by interstitial cystitis patients, their age at diagnosis, the female-male ratio and disease history were in line with those reported in other European and American studies⁸,¹⁰-¹³.

Approximately 90% of Dutch urologists used 3 or more criteria to diagnose interstitial cystitis, while 26% used the interstitial cystitis criteria as defined by the NIH of the United States⁶. A small group of 13 urologists used 2 (9) or only 1 (4) diagnostic criterion. However, this subgroup did not show any consistent preference for any single criterion.

Although a wide variety of oral and intravesical therapeutic possibilities are available¹⁰,¹⁴,¹⁵, Dutch urologists appeared to follow a fairly uniform therapy policy. Of the Dutch urologists 50% preferred dimethyl sulfoxide instillations as the initial treatment option, while 30% used dimethyl sulfoxide as a second or third line treatment. The same findings applied to prolonged, static bladder distension. Although the efficacy of hydrodistension according to Helmstein has been questioned by some¹⁶, it proved to be a rather popular treatment in The Netherlands. Treatment policy was not influenced by difference in geographical region, diagnostic criteria or number of interstitial cystitis patient consultations per year.

Surgery was considered by 88% of the urologists as a (final) treatment option. In contrast, 18% of the urologists reported not ever performing surgery on interstitial cystitis patients. This difference could be the effect of asking for estimations on a questionnaire instead of performing a thorough retrospective study. In addition, 39% of the urologists performed surgery in 5%, 26% in 5 to 25%, 8% in 25 to 50% and 9% in more than 50% of the interstitial cystitis patients. No significant differences between the subgroups and the total group existed concerning region, number of interstitial cystitis patients treated in 1993 or diagnostic criteria used. It was not possible to determine the success rate of surgery. The use of different surgical techniques reflects the controversies reported in the literature¹⁷,¹⁸.
CONCLUSIONS

The prevalence of interstitial cystitis in the Netherlands is estimated at 8 to 16 cases per 100,000 female adults, which probably is a conservative estimate since only interstitial cystitis patients who sought treatment were reported. Mast cells had an important role in the diagnosis of interstitial cystitis and were reported by 80% of the Dutch urologists as a diagnostic criterion. Difference in definition and awareness of interstitial cystitis could explain the difference in prevalence of interstitial cystitis. Dimethylsulfoxide instillations and hydrodistension of the bladder were practised by more than 80% of the Dutch urologists. This fairly uniform therapy preference demonstrates a remarkable consensus among Dutch urologists concerning interstitial cystitis.

REFERENCES