

Forming a Non-Profit Organization for Patients with a Urological Disease in 1984: Does it relate to Clinical Microbiology Today?

Vicki Ratner*

Founder and President Emeritus, Interstitial Cystitis Association of America, VA, USA

*Corresponding author: Vicki Ratner, Founder and President Emeritus, Interstitial Cystitis Association of America, 1760 Old Meadow Road, Suite 500, McLean, Virginia, USA, Email:VRatner@aol.com

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Abstract

Interstitial Cystitis (IC), also known as Painful Bladder Syndrome (PBS), was initially described in the mid 1800's. It was not until 1984 that a patient non-profit organization, the Interstitial Cystitis Association (ICA), was formed in order to work with IC patients and the National Institutes of Health (NIH) to define and increase research on this enigmatic and debilitating condition. The media played an important role in bringing together patients and helping them understand that they were not alone in their suffering. Epidemiological studies legitimized the disease and research at the NIH and other academic institutions progressed enormously. However, despite over 30 years of hard work, urologists have been unable to determine a cause for IC or any truly effective treatments to help patients suffering from this condition. Collaboration with other specialties, in particular clinical microbiology, may prove fruitful in advancing research into the cause and potential treatments for IC.

Keywords: Interstitial Cystitis; Painful bladder syndrome; Urinary tract infection; Pentosan polysulfate sodium; Familial crohn's disease

Introduction

In 1983, as a third year medical student, I developed severe suprapubic pressure, urinary urgency and frequency and a burning pain in my bladder. The pain felt like a lit match in my urethra. I was barely able to function, and found it almost impossible to concentrate due to the pain. I assumed I had a Urinary Tract Infection (UTI), but a complete work-up was negative and antibiotics failed to relieve the symptoms. In search of a diagnosis and relief from the severity of these symptoms, I sought advice and assistance from 14 physicians, most of whom told me that there was nothing that they could do to help me. Some suggested that I was not cut out to be a physician that I should drop out of medical school, get married, and settle down into a more traditional lifestyle. I spent the last two years of medical school in intense, unremitting pain and isolation, imagining that I was the only one in the world suffering with this disease [1]. Eventually, I went to the medical library. I turned to Campbell's Urology, the standard

Urological textbook, where I learned that IC was considered a rare post-menopausal condition and also found it included in the psychosomatic section of the text. "IC may represent the end stage of a bladder that has been made miserable by emotional disturbance: A pathway for the discharge of unconscious hatred" [2].

Using index medicus at that time, I found an article that led me to the diagnosis of IC [3]. A cystoscopy under general anesthesia confirmed the diagnosis of IC using criteria from the article. While it was an enormous relief to have a diagnosis, the only available FDA approved treatment at that time was intravesical Dimethyl Sulfoxide (DMSO), which provided no relief for my symptoms. Then I tried pentosan polysulfate sodium (Elmiron) (available under the Compassionate Use Act), an oral medication eventually approved by the FDA in 1996 for treatment of IC. Elmiron provided no relief for me either. It has dramatically helped a relatively small percentage of IC patients. Unfortunately, in 2018, long-term use of Elmiron has led to a unique pigmentary maculopathy of the eyes and in some cases has led to loss of central vision which is not reversed by discontinuance of the drug [4].

I was left to live with severe pain and nowhere to turn to for help. I decided to try to find other patients with the same condition and turned to the media to publicize my situation. Dr. Philip Hanno of the University of Pennsylvania and I were interviewed on ABC's Good Morning America in 1985. After a five minute interview on this show, within one week, The ICA received over 10,000 letters, mostly women and some men who were having the same symptoms as I did. Here is an example [1].

"I am a nurse and I have interstitial cystitis. It took over 15 doctors and over 2 and half years to even get a diagnosis. Needless to say, 14 doctors didn't believe me and recommended psychiatric care. I knew something was wrong and persisted. I haven't been able to work for 2 years, I have an intense unrelenting pain and as hard as I tried mentally, physically and emotionally, I cannot stand it for long without relief. I feel like I am being tortured without respite. It makes your life an endurance contest [5]."

I found several women with the same bladder symptoms as I did, and we decided to form a non-profit organization, the Interstitial Cystitis Association (ICA). The goal of the ICA was to assist IC patients and advance research into the cause and cure

for IC. The ICA website (www.ichelp.org) was set up in the early 1990's, and as word got out, we were receiving over 1 million hits/day. We raised funds to set up an ICA pilot research grant program, and 40% of the grant recipients over the years went on to receive research funding from the National Institutes of Digestive, Diabetes and Kidney funding (NIDDK) (Bladder conditions are under the division of kidney diseases).

Subsequently, I was interviewed by Jane Brody of the New York Times, many other major newspapers nationwide, the Associated Press, CNN, NPR and almost all of the women's magazines. This brought in hundreds of thousands of letters from IC patients. Despite the outpouring of attention and letters, we still had no 'proof' that this was not a rare disease or that it was a disease at all.

Advocacy and Research Progress

Although one of the earliest articles on IC was published in 1887 [6], research in earnest in the United States did not begin until the first NIH conference on IC was held one hundred years later in 1987.

The first epidemiology study on IC in the United States was undertaken in the late 1980's by Dr. Philip Held at the Urban Institute, shortly after the NIH conference. He found, surveying nearly 1,000 patients, that for every patient diagnosed with IC, there were 5 others who had the same symptoms yet remained undiagnosed. For IC patients, it took an average of 4.5 years and five physicians to achieve a correct diagnosis. IC patients scored worse than patients undergoing renal dialysis on "Quality of Life" questionnaires. A total of 60% of IC patients reported pain with sexual intercourse, many so severe that they abstained from sex altogether. Held's study calculated the economic impact of the disease, taking into account medical expenses and lost wages incurred by IC sufferers, to be as high as \$1.7 billion per year [7]. The Held study estimated 90,000 women had IC.

For the following 20 years, conferences on IC were sponsored by NIDDK biannually. The American Urological Association (AUA) began holding seminars on IC at their annual meetings as well as moderated poster sessions which they continue to do today. Through the efforts and perseverance of many IC patients and researchers, IC finally was legitimized as a genuine and distinct disease, with symptoms that vary from mild to severe and from intermittent to constant. Today we know that in United States 3.3-7.9 million women (the authors of this study believe this is an underestimation), and 1-4 million men have IC [1,8,9].

We learned a tremendous amount from other organizations especially from "The National Organization of Rare Diseases", founded by Abbey Meyers. Setting up a strong Medical Advisory Board was essential to the ICA. Lobbying was critical, as was finding a Congress person to take up our cause. We were fortunate to work with Senator Harry Reid from the early 1990's until his retirement in 2017. Testifying before Congressional hearings at the Department of Health and Human Services (HHS) each year was an absolute necessity. Our testimony, which was reviewed by HHS, was summarized and placed into the Congressional Report that directed NIH on how to spend the funds allocated by Congress. Each year, we received a few more

sentences about IC in this report, and within a few years, one million dollars was allocated specifically towards the study of IC. This amount went up substantially over the years [1].

Despite tremendous efforts over the decades by a large cadre of urologists and researchers, we still do not know what causes IC, nor are there any new treatments that truly relieve the symptoms of IC patients.

Relating Clinical Microbiology to IC

We know that many patients with IC may have associated conditions, such as vulvodynia, irritable bowel syndrome, Crohn's Disease, Chronic Fatigue Syndrome, and a host of other conditions [11]. Crohn's Disease might be an area for urologists to look at because the gastrointestinal lining is very similar to the urothelial lining of the bladder. Pathologic extracellular organisms have been identified on the cells lining the gastrointestinal tract, but have yet to be evaluated on the urothelial lining of the bladder.

Familial Crohn's Disease is an area that could be explored for some answers. In 2016, researchers reported the presence of three organisms (*Candida tropicalis*, *Escherichia coli*, and *Serratia marcescens*) on the gastrointestinal lining [12]. More recently, it was shown that the above three organisms were found in elevated amounts in a cohort of patients with Crohn's Disease. Thus far, antibiotics and anti-fungal medication have not been effective in penetrating the microbiome/mycobiome of these organisms.

Urologists have continued to use the same urine analysis and culture for the past 70 years, and on the basis of this have ruled out bacteria as implicated in IC. But what if we took urine samples from IC patients, spun them down, poured off the supernatant, and examined the urothelial cells under a confocal scanning laser microscope (usually found in gastroenterology departments) to determine whether there were any bacteria or fungi attached to the urothelial cells (personal communication with Dr. Mamoud Ghannoum, Case Western Reserve University) [13]. If there were positive findings, a larger scale study could be initiated to validate the pilot study. The next step could be to create specific phages (lytic viruses) that could penetrate the biofilms of specific organisms that might be found on these urothelial cells, followed by administration of appropriate medication [14].

A search for other pathologic extracellular organisms on IC urothelium using modern investigative techniques by clinical microbiologists may prove enlightening. It may hold the key to identifying at least some etiologies of IC and could lead to treatments that may dramatically reduce symptoms or possibly lead to a cure.

Conclusion

It is important to keep in mind how far we have to go, how much misery IC still causes, and how many hundreds of thousands of lives IC continue to be ravaged by this disease. The pain from IC can be so intolerable that some patients have been driven to take their own lives. Treatments and a cure are

urgently needed, yet little genuine help for IC patients has been found, even though hopes were raised by the first NIDDK conference held in 1987. We hope that clinical microbiologists will be interested in following-up on possible parallels between IC and Familial Crohn's Disease, and pursue other strategies or new techniques that may advance research on IC.

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