Interstitial Cystitis Epidemiology Task Force Meeting
National Institute of Diabetes and Digestive and Kidney Diseases
Democracy 2, Room 701
October 29, 2003

Meeting Report
Draft

Members of the Interstitial Cystitis (IC) Epidemiology Task Force, the IC Executive Committee, ad hoc participants, and National Institutes of Health staff met in Bethesda, Maryland, October 29, 2003, to review the status of current investigations of IC and to plan new epidemiology investigations. In his welcoming remarks, Dr. Griffin Rogers, deputy director of the NIDDK, described the overarching goals of the meeting: "The Task Force has come together to review, on the best available evidence, what is known and what is not known about IC, so that ultimately we can turn data into knowledge and knowledge into action." Dr. Rodgers assured participants that their recommendations would be taken seriously in the upcoming fiscal year and beyond.

Executive Committee co-chairs, Dr. E. Darracott Vaughan and Dr. Timothy Wilt, urged the Task Force to think "outside the box" and to avoid preoccupation with a definition of IC early in the meeting. The definition would emerge in breakout group discussions, Dr. Vaughan said. He called on the group to help determine the best methodology for an epidemiology study, the best available instruments, and the adequacy of those instruments. Dr. Wilt told Task Force members from disciplines outside urology that their contributions to the meeting would be critical.

After a morning of presentations that reviewed the past and present status of IC research and potential models for future studies, Task Force members formed two separate groups and adjourned to meeting rooms for a working lunch and several hours of discussion. A summary of the meeting presentations and breakout group reports follows.

Presentations

Definition and Diagnosis: Where We Are in 2003

Dr. Phillip Hanno set the stage for the meeting in his presentation on the history of IC and attempts to define and diagnose it. Paraphrasing Anthony Walsh, Dr. Hanno described IC as "a disease of extremes—extremes of severe symptoms, of under diagnosis and over diagnosis, of etiologic theories that vary from the abstruse to the fashionable, of treatment that varies from the alpha of vitamin prescriptions to the omega of radical bladder substitution surgery, and sadly often, of confusion in medical thinking."

The pursuit of a definition and diagnosis of IC began in 1887 when Skene described the disease as an inflammation of the bladder that destroyed the mucosa and extended to the

muscular parieties. In 1915, Hunner described an ulcer; however, the failure of physicians to subsequently find Hunner's ulcers hampered diagnosis until modern times. Glomerulations—small, discrete purple hemorrhages of the bladder mucosa that are often found in IC patients—were first described in 1949 during cystoscopy.

In 1987, the NIDDK convened a conference to define IC criteria that could be used to select a core group of patients for comparative clinical and basic science research. The NIDDK criteria were further refined in 1988 (Attachment).

Although the NIDDK's criteria were meant strictly for research, physicians subsequently used them to make a clinical diagnosis. Consequently, many patients whose symptoms did not meet the criteria were not diagnosed. In 1999, a review of the NIDDK database findings for IC found that expert clinicians would have diagnosed 50 percent of the patients who were excluded by the criteria. In the 1990s, the NIDDK's Interstitial Cystitis Data Base (ICDB) and the Interstitial Cystitis Clinical Trials Group (ICCTG) modified the criteria to make them more inclusive.

Today, IC is commonly thought of as a clinical syndrome defined by its symptoms—urgency, frequency, and/or pain in the absence of any causation. Because this is a symptom-based definition, semantics can become an issue, Dr. Hanno said. Pain, for example, may be described by some patients as intense pressure or discomfort.

Finding a marker that distinguishes IC from conditions that mimic it, such as carcinoma in situ, scleroderma, and bladder instability, would enable a definitive diagnosis in the face of competing potential etiologies. A marker would also provide insight into the etiology and pathogenesis of the disorder, allow for a rational treatment algorithm, improve data on long-term prognosis, and/or serve as an adjunctive measure that follows the clinical course.

In the absence of a marker, IC is a diagnosis of exclusion. The symptoms of a number of diseases and disorders such as bladder instability are similar and must be ruled out. Physicians with expertise in diagnosing and treating IC are usually able to make the diagnosis based on symptoms alone, although cystoscopy with hydrodistention is useful to confirm a diagnosis of IC, to exclude other benign or malignant diseases, or to determine more aggressive treatment. However, glomerulations and ulcers also occur in radiation cystitis, chemotherapy, exposure to toxic chemicals, and incontinence. Glomerulations are sometimes present in normal patients, as well. For 35 percent of IC patients, hydrodistention can be beneficial; it provides a reduction in symptoms for six months or more. However, the procedure is not without risks—it must be performed under anesthesia because it is painful.

Urodynamic tests are not necessary for a diagnosis of IC, but they are useful to diagnose sensory urgency and detrusor instability, which have similar symptoms and also coexist in 15 percent of IC patients. Treatment with anticholinergics can help those patients who do not have IC or patients who have these disorders along with IC.

The potassium chloride sensitivity test, a simple, inexpensive, office-based test, has been considered by some clinicians to be useful in making a diagnosis of IC, but it is not essential for a definition of the disorder. The test is positive in 80 percent of IC patients. In 20 percent of IC patients, the test has a false negative response, which also occurs in 4 percent of normal subjects. Additionally, the test has a 25 percent false positive rate in patients with detrusor instability, and a 100 percent false positive rate in women with urinary tract infections. At best, the PST is a test for bladder sensitivity of undetermined origin. The PST is painful in patients who test positive, is not specific to IC, and does not predict response to treatment; therefore, the PST has not been recommended for diagnostic purposes.

Studies on the prevalence of IC have produced a wide range of estimates. The Held study, the first population-based study of IC in the United States, estimated that a half million Americans may have IC. The study also reported an increased incidence of Crohn's disease and lupus erythematosus in IC patients. Using the potassium sensitivity test as a reference standard, Parsons has concluded that 22 percent of all women in the United States have IC.

Many questions about IC remain to be answered, Dr. Hanno said. For example,

- Is IC a bladder disease, an infection-initiated/promoted disease, a nervous system disease, or a barrier problem?
- What is the role of mast cells, hormones, and other immunologic or molecular mechanisms in IC?
- Is there a barrier problem in some or all IC patients?
- Is IC one disease or an end point of a variety of etiologies?
- What is the minimum data set to make a diagnosis of IC?
- Is there a different data set for noninvasive treatment than for invasive treatment?
- What has to be excluded to diagnose IC?
- Should ulcerative forms be considered different from non-ulcerative forms?

Because the symptoms of IC are similar to several other syndromes, investigators have begun to question whether consolidation of several syndromes into one definition can be useful for IC research. For example, Chronic Pelvic Pain Syndrome (CPPS) in men, CPPS in women, dyspareunia, and IC, have similar symptoms, and many men who have CPPS may also have IC. Overactive bladder overlaps with IC as well, and patients with urethral syndrome, urethritis, and trigonitis often develop IC.

A consolidated definition of IC might be indicated when the

- Underlying etiology is similar
- Underlying pathology is the result of numerous similar etiologies
- Treatment algorithm is the same
- Underlying epidemiology suggests similarity
- Prognoses are similar
- Natural history suggests a single entity

For example, many physicians and investigators believe that Chronic Pelvic Pain Syndrome in men (nonbacterial prostatitis) can be explained by some underlying unity with IC. However, Dr. Hanno believes that basic clinical and epidemiological research findings are not available to support consolidation at this time.

Studies of several chronic illnesses associated with IC can be examined for guidance on how to proceed in an IC epidemiological study. Irritable bowel syndrome (IBS) is similar to IC in that the diagnosis must be made based on symptoms because of an unknown etiology. Treatment for IBS is also based on symptoms in the absence of empiric data. Studies estimate that 22 percent of IBS patients have IC, and 15 percent of IC patients have IBS. Studies of fibromyalgia and Sjögren's syndrome would also be useful for similar reasons.

To summarize what is empirically known about IC, Dr. Hanno reviewed past epidemiological studies.

- The 1975 Orovisto (Finnish) study, the first major epidemiological study of IC, concluded that 90 percent of IC patients are women; the prevalence is 18.1 women per 100,000; and 10 percent of cases are severe. The study also reported that most women had rapid onset of symptoms, rapid progression, and then stabilization. The study estimated that a diagnosis of IC was not made for three to five years.

- The 1987 Held et al. study, the first epidemiological study of IC in the United States, estimated that based on symptoms alone, the United States has 43,000 to 90,000 diagnosed cases—two times the prevalence estimated by Orovisto. The study also estimated that up to 500,000 people in the United States have IC; IC patients have double the incidence of UTIs compared to controls; the median age of onset is 40 years old; and 50 percent of patients experience spontaneous remission for a mean of eight months.

- The Curhan et al. study, a population study of two cohorts of registered nurses from the National Nurses Health Study, reported a prevalence of IC in U.S.

women of 52 per 100,000 in the first cohort (NHS I) and 67/100,000 in the second cohort (NHS II).

- The Interstitial Cystitis Association survey (ICA Study Group) reported that persons with IC had a higher prevalence of fibromyalgia, Crohn's disease, colitis, and lupus than the general population.

Much more epidemiological data is needed on IC and other syndromes in the IC family before concluding that they are all one and the same, Dr. Hanno said. Population-based studies are accurate but expensive; however, they would help delineate risk factors and prevalence. Case-controlled studies could be used to identify IC patents and to match them with controls. Coordinate-incidence case studies could help with understanding the natural history and etiology of the illness. Basic science studies are also needed for this purpose.

"Case-control studies might be a cost-effective way to identify risk factors, demographic features, familial aggregations, and associated syndromes," Dr. Hanno said. "Most important are longitudinal studies of the natural history of IC. We don't know the natural history. Do some patients get well without treatment? When does this disease become chronic? Will early diagnosis affect outcome?"

Lessons from Chronic Fatigue Syndrome

Dr. William Reeves discussed the pursuit of a diagnostic definition and the epidemiology of Chronic Fatigue Syndrome (CFS) by the Centers for Disease Control and Prevention (CDC). Dr. Reeves said that on listening to Dr. Hanno's presentation, he was struck by parallels between IC and CFS. Both illnesses appear to involve alterations of complex symptoms and mind-body interactions, that is, interactions between the central nervous system and other organ systems.

Dr. Reeves described CFS as a debilitating, disorder, characterized by profound, all-encompassing fatigue. It primarily affects women, and two recent population-based studies conducted in Chicago and in Wichita have determined prevalence to be between 300 and 600 per 100,000 adults, 18 to 60 years old. There are approximately 800,000 cases of CFS in this country.

The average duration of CFS differs in population-based studies (5 years) versus clinic-based studies (8 to 10 years). Of interest to IC investigators, Dr. Reeves said, is the finding that physicians diagnosed fewer than 20 percent of the people who met the strictest criteria for CFS. "Eighty percent of the cases, and I would not be surprised if this were true for IC as well, have not [been] seen [by] a physician," Dr. Reeves said, adding that this is the reason why randomly sampled population-based studies are needed. Although more expensive, they are much more accurate and representative.

In the early 1990s, almost all CFS studies were clinic-based. As a result, CFS was characterized as a disease that primarily affected white women in their 40s and 50s, who were in the middle to upper socioeconomic groups. The women were well-educated

professionals who developed sudden onset of symptoms. The CDC eventually conducted community studies, which confirmed that the majority of CFS patients were women in their 40s and 50s; however, these studies estimated that the minority population has twice the prevalence of CFS. The studies also concluded that CFS is more common in the lower socioeconomic strata and that slow onset of illness occurs equally as often as sudden onset.

Dr. Reeves explained that another problem with clinic-based studies is that each study used a different definition of the illness and that symptoms were self-reported and not uniformly assessed. He advised the Task Force that these drawbacks of clinic-based studies must be considered when planning IC studies.

According to Dr. Reeves, the definition of CFS has changed during the past 10 years in much the same way that the definition of IC has changed. In 1994, the International CFS Study Group, convened by the CDC, developed criteria based on consensus clinical opinion, in much the same way and for many of the same reasons the NIDDK criteria were developed in 1987—that is, to standardize patients for research studies. The problem with the CFS criteria was that they were not specific enough and not empiric-based. For example, one of the criteria stated that the research subject must have at least four of eight symptoms, among them, impaired concentration or memory and post-exertional worsening of physical or mental fatigue. "The accompanying symptoms need to be defined in and of themselves," Dr. Reeves said. The 1994 International Study Group also hypothesized that fatigue led to patients' symptoms rather than the reverse.

The CDC is currently conducting population studies to develop an empiric definition of CFS that is based on statistical modeling. These studies show that people with CFS have an illness with three closely correlated factors:

- Cognition loss/sleep loss
- Musculoskeletal problems
- Inflammation and infection

As a result of these findings, investigators are beginning to consider fatigue as an end product rather than a causal factor of CFS.

Today, the CDC CFS Research Program strategy is to conduct population-based studies. So far, the program has conducted three studies and a fourth is in progress. The cost of the latter is between $6 million and $8 million. The CDC's CFS Research Program's strategy is as follows:

- Conduct a population survey with screening telephone interviews of household informants.

- Randomly select a cohort of volunteers identified as well or unwell with fatigue based on the interview.

- Re-contact and interview subjects in detail, using questionnaires developed for telephone use. The interview covers demographics, a description of fatigue, occupation, and socioeconomic information, and the interviewer uses a questionnaire that describes a variety of symptoms. The interviewer also screens for exclusion criteria, medical and psychological conditions, comordid psychiatric conditions, and lifetime experiences. The latter is important, Dr. Reeves said, because one of the hypotheses of the study is that accumulated stress might be an extremely important factor in CFS. He said this might be the case for IC as well. About 22 percent of the persons interviewed will have an exclusionary condition.

- All people identified as being unwell with CFS-like symptoms are invited to a clinic for a one-day, one-on-one evaluation. In addition, randomly selected, unwell people with non-CFS-like symptoms are also invited for a clinical evaluation. All those who come to the clinic are given medical and psychological evaluations and their symptoms are evaluated using standardized instruments. A variety of laboratory studies are done, as well as psychiatric assessments. In addition, volunteers are evaluated for economic impact and access to health services. Generally, 75 percent of the people selected respond, and about 30 percent are excluded from the study after the clinical evaluation is performed. Subjects with CFS symptoms are matched by sex, race, ethnicity, and age with a control group and with a group that has symptoms of fatigue from other illnesses.

- These cohorts can then be used for cross-sectional, GCRC, or in-patient clinical studies

Laboratory studies performed by the CDC in this research strategy are to determine risk factors and diagnostic markers and are particularly applicable to IC, he noted.

Dr. Reeves explained that case-control studies do not work well if the condition being studied is not a disease—a single pathologic entity—but rather a complex illness or a similar response to a variety of causes. CFS is a complex illness that is not necessarily the result of a single mutation or a single environmental factor. He suggested that probably a combination of genes, environmental factors, and risk-conferring behaviors are involved. “Understanding [CFS], may elucidate similar pathways for other diseases,” he said, adding that he looks at CFS as a mind-body interaction because many of the symptoms are central nervous system symptoms, but the musculoskeletal, immune, and gastrointestinal systems are also involved.

Using genomics and proteomics, the CDC has launched a program of diagnostic biomarker discovery that will provide insight into the pathogenesis of CFS and lead to hypothesis-driven research. Results from gene expression profiles show that CFS cases with gradual onset cluster together and cases with sudden onset do the same. The differentially expressed genes represent a small number of pathways, he said, and among

them are extracellular transport, immune system, and cell-surface antigens. The majority of cases have distinct protein profiles when compared with the controls.

Dr. Reeves said that the CDC originally intended to do a national population-based study but realized that conducting clinical evaluations nationwide would be a problem because of the cost and the difficulty in standardization of the procedures. A national pilot study showed that there is virtually no difference geographically among the urban centers and among the rural areas. Wichita, Kansas, was selected because, according to census data, it is similar to the U.S. population in all areas. Georgia, where the CDC is located, was selected because it has a well-defined urban population in the Atlanta metropolitan area and well-defined rural populations within two hours driving time. Georgia also has a large Hispanic and black population in both urban and rural areas.

Epidemiological Research: What Do We Know about IC

Dr. Gary Curhan reviewed previous epidemiological studies of IC, which had a wide range of prevalence estimates from 16 to 450 per 100,000. He attributed the wide range of estimates to different research definitions, different populations and different study designs. Several of the studies are as follows:

- Oravisto study, Finland (1975): The cross-sectional survey of a single urology practice in the province of Uusimaa, which includes Helsinki, reported a prevalence of 19 women per 100,000. Dr. Curhan noted that the survey may have interviewed only the most severe cases who sought treatment from a specialist.

- Held study, United States (1987): This cross-sectional study estimated a prevalence of 38 women per 100,000. The study surveyed 127 urologists; 64 IC patients selected by the random sample of urologists; 902 women who were members of the Interstitial Cystitis Association; and 119 persons (73 female) from the U.S. population. The study surveyed a possibly biased sample, Dr. Curhan noted, because 26 percent of the respondents were urologists, and because the study's reported incidence and prevalence rates were not internally consistent. The study was not published in a peer-reviewed journal.

- Bade study, Holland (1995): The cross-sectional survey interviewed urologists and reported an incidence of 8 to 16 per 100,000. The sampling strategy resulted in a biased sample.

- Jones study, US NHIS (1997): The cross-sectional study of the U.S. population that surveyed participants for self-reports of a diagnosis of PBS (PBS) or IC reported a prevalence of 870 per 100,000. The definition was vague and the study emphasizes the prevalence of PBS.

- Ito study, Japan (2000): The cross sectional survey of Japanese urologists reported a prevalence of IC as 4-5 women urology patients per 100,000. Diagnostic criteria were not uniform, no males were included, and there was no population-based denominator.

In 1999, Dr. Curhan conducted a population-based cohort study of IC. He surveyed two cohorts of female registered nurses enrolled in the National Nurses Health Study (NHS). NHS I, a study of 121,701 nurses, ages 30 to 55, from 11 states, began in 1976. NHS II began in 1989 and enrolled 116, 671 female RNs ages 25 to 42, from 15 states.

Nurses who self-reported interstitial cystitis in a 1994 NHS I questionnaire and in a 1995 NHS II questionnaire were selected for the Curhan study. The 1994 questionnaire asked the nurses whether IC had ever been diagnosed with cystoscopy. The 1995 questionnaire asked whether participants had ever been diagnosed with interstitial cystitis. Curhan et al then sent the nurses who self-reported IC a supplementary questionnaire to collect additional information and a permission form for access to their medical records. Accuracy of the nurses' reports was assessed using a version of NIDDK's diagnostic criteria for research studies. These criteria were modified and broadened for the study to avoid exclusion of women who had milder symptoms of the illness. The modified criteria included a cystoscopy with or without hydrodistention for symptoms of IC; diagnosis of IC documented in the medical record or in the absence of that, in a physician's letter; no history of bladder cancer, radiation to the pelvis, and cyclophosphamide use. Confidence in the certainty of the diagnosis was divided into three categories of definite.

Prevalence for the NHS I women was 52 per 100,000, and for the NHS II women, 67 per 100,000. The study concluded that interstitial cystitis is more than 50 percent greater in the United States than previously reported and three-fold greater than prevalence reported in Europe. In the NHS I cohort, the mean delay-to-diagnosis was 7.1 years; in the NHS II cohort, the mean delay-to-diagnosis was 5 years. Two other findings of the Curhan study are as follows: (1) IC not only affects middle-aged women, but also younger and older women with approximately equal frequency; (2) self reports of IC are not sufficient to determine the diagnosis of IC. Dr. Curhan also noted that the study is not representative of the U.S. population since 95 percent of the participants were white professionals.

Dr. Curhan noted that one of the problems of self-reported IC is that symptoms fluctuate. The information reported depends on when the questions were asked. Before future studies of IC are performed, investigators need to develop a better research definition of chronic pelvic pain of the bladder or IC. Dr. Curhan emphasized that studies should not just focus on those who have pain, because many other persons with IC will be missed. "Phil Hanno described the definition quite well as frequency, urgency, and/or pain. At least 30 percent do not have pain," Dr. Curhan explained.

Future studies are needed, he said, to provide more precise prevalence and incidence estimates, to identify risk factors for initiation and progression, and to explain the natural history. Studies are also needed on exposure before onset of symptoms, genetic factors, sex differences, socioeconomic impact, race, ethnicity, and age, and associations of IC with other conditions.

NIDDK Current Work: Interstitial Cystitis Database

Dr. Kathleen Propert described the Interstitial Cystitis Database (ICDB), a prospective cohort study of 673 patients with IC who were enrolled in the study from January 1993 to January 1997. The goals of the study were to assess demographic and clinical characteristics of patients with IC, examine treatment patterns, and evaluate the natural history of the disease.

Criteria for inclusion in the study were based on the 1987 NIDDK criteria for research studies of IC, that is, all patients had symptoms of urgency, frequency, and/or pelvic pain for at least six months before the study, but a baseline cystoscopy was not required. The broadening of the criteria was necessary, Dr. Propert said, because the sensitivity of the criteria is not very good; therefore, a lot of cases have been missed. The specificity of the NIDDK criteria is 90 percent, however.

Ninety-one percent of patients were female and 93 percent were white. Median age was 43 years. Females were younger than males; the median age for females was 42 years, for males, 53 years. During the study, patients received treatment by their clinicians according to usual clinical practice. The study used a pain/urgency/frequency score to gauge the severity of symptoms: 7 percent presented with mild symptoms, 44 percent presented with moderate symptoms, and 49 percent presented with severe symptoms. Severe urgency and frequency were more common than severe pain. Symptoms fluctuated with time for many patients who had the characteristic remission and flare up of symptoms; yet, despite the variability, little or no long-term change in symptoms was observed in a four-year period. The ICDB study concluded that IC is a chronic disease that severely reduces quality of life.

When the ICDB cohort was subsequently compared with the cohort of men who have chronic prostatitis, another disorder characterized by pain in the bladder region, women with IC had a much higher incidence than men and the population in general of associated diseases such as fibromyalgia. In addition, when the voiding diaries of IC patients, chronic prostatitis patients, and the general population were compared, voiding patterns were consistently different between men and women and between IC patients and other groups. Women and IC patients had more voiding symptoms. Older men appeared to have symptoms similar to chronic obstruction rather than to chronic prostatitis or IC.

NIDDK Current Studies: Northwestern University /Kaiser Study of Chronic Bladder Symptoms

Dr. Quentin Clemens described the Northwestern/Kaiser study as “a population-based study of the prevalence of chronic bladder symptoms, including IC,” in men and women enrolled in a Kaiser Permanente Health Maintenance Organization (HMO) in Portland, Oregon. Northwestern selected the HMO because its research arm was capable of conducting this type of research. The HMO’s database contains information on 440,000 patients whose data are entered by clinicians into an EPIC electronic medical record. CPT codes are also recorded. The HMO has a stable population and 93 percent of patients are white.

After an initial search of the database in May 2002 to exclude patients with other diagnoses, a patient cohort was formed consisting of 136,400 women and 125,553 men. Studies of the database were conducted using different criteria for IC. Based on a CPT code for IC, for example, prevalence for women was estimated to be 197 per 100,000, and for men, 41 per 100,000. When NIDDK study criteria were applied, the prevalence for women dropped to 158 per 100,000 and for men, 28 per 100,000. Using a definition of IC that required a cystoscopy of any type, prevalence in women was reported as 99 per 100,000 and in men, 19 per 100,000. Despite whatever definition was used, the male to female ratio was 5:1.

The next step of the Northwestern/Kaiser study will involve sending questionnaires to patients with IC. The questionnaires will ask about symptoms of urgency, frequency, and pain. The BPSI will be sent to men and a modified version will be sent to women. The Likert scale will be used to assess severity of symptoms.

NIDDK Current Studies: Boston Area Community Health (BACH) Study

Dr. William McKinley presented the study design and methods used in the BACH epidemiological study and the progress to date. The BACH study is large, community-based study that is surveying persons in the Boston metropolitan area to determine the prevalence of symptoms of interstitial cystitis, benign prostatic hyperplasia, prostatitis, urinary incontinence, hypogonadism, and erectile dysfunction. The study's goal is to recruit 6,000 subjects, ages 30 to 80, from four neighborhoods in the Boston area that have density levels proportionate with minority populations. Half of the subjects in the study will be men and half will be women; one third of the study population will be Hispanic, one third African American, and one third Caucasian.

The four neighborhoods have been divided into 12 strata and from them investigators are selecting census blocks. Households are then randomly selected from the census blocks and sampled to identify eligible study participants. Dr. McKinley noted that the BACH study has a unique design that involves sampling in batches of 1,000. Each batch is a random sample of the overall study population. "The advantage of this method is that it keeps logistics manageable and allows the adjustment of sampling fractions at different levels as you go to achieve the representation you want," he explained. For example, in the first batch, investigators took 200 blocks, selected 6,000 households, and from them identified 1,730 people, of whom 953 were identified as eligible participants. In a second batch, they identified 948 eligible participants, and in a third batch, 540 eligible participants.

Investigators conduct a 2-hour, in-home, bilingual field interview of all eligible participants, looking at symptoms and asking questions about lifestyle, physical activity, alcohol use, nutrition, demographics, and morbidity. They also conduct a detailed inventory of medications, both prescribed and over-the-counter, and take two non-fasting blood samples that will be stored for future studies.

Dr. McKinley said that comparison with data from NHANES indicates that the BACH population is representative of the Northeast and a study of whether it is representative of the entire U.S. population is currently underway.

Designing an epidemiological study of IC is a challenge for an epidemiologist because of the symptom variability, Dr. McKinley said. Some patients do not recognize IC as a problem and some providers do not diagnose it; therefore, it is necessary to perform symptom-based research. Also, some patients do not receive a diagnosis or treatment because they do not have access to health care. "Some of the differentials in race and ethnicity [that] we are seeing in [the BACH] study so far may have a lot to do with differential utilization of the health care system by race and ethnicity," Dr. McKinley said.

NIDDK Current Studies: University of Maryland Case-Control Study of IC

Dr. John Warren described the University of Maryland School of Medicine study as an incidence study of IC. NIDDK criteria as modified by the Interstitial Cystitis Clinical Trial Group (ICCTG) will be used in the study to identify 400 patients who have had symptoms of IC for 12 months or less. Random digit dialing will be used to identify all participants in the study, who will then be interviewed by telephone. Investigators will match patients with symptoms of IC by age and sex to controls. A questionnaire will be mailed to eligible participants and the medical records of volunteers will be reviewed.

The first goal of the University of Maryland Case-Control Study is to identify risk factors and clues to the pathogenesis of IC. Investigators hope to identify exposures to environmental factors prior to the onset of symptoms. The study will also examine diseases associated with IC such as irritable bowel syndrome and the potential use of antiproliferative factor, a biomarker identified by Dr. Susan Keay in a study of IC patients. Antiproliferative factor was present in 95 percent of patients with IC and in less than 10 percent of controls. Investigators hope that the biomarker can be used to diagnose early onset. The fourth aim of the University of Maryland study is to provide a cohort of patients who can be followed through time to elucidate the natural history of IC.

Discussion of Presentations

During the discussion period following the presentations, Task Force members discussed the advantages and disadvantages of the studies that were presented in the morning session. The definition of IC for diagnosis in research studies was a primary concern of Task Force members. Simply asking subjects whether they had ever been diagnosed with IC has not been useful in the past because they may confuse IC with bacterial cystitis.

Although most Task Force members agreed that the simple symptom-based definition of IC as frequency, urgency, and/or pain in the absence of any other reasonable causation would include most people with IC, self-reports of symptoms are subjective and difficult to assess. What is pain to one person may be described as discomfort or pressure by another. Also, urinary frequency varies widely in people, depending on their bladder capacity and intake. In addition, not enough is known about normal variability to establish a cut-off between normal and abnormal frequency. In addition, the urgency

experienced by IC patients, which is driven by bladder pain, should be distinguished from the urgency experienced by patients with urinary incontinence, which is driven by fear of losing bladder control.

Location of pain was another issue. Some survey or interview questions located pain in the pelvis or in specific areas of the pelvis such as the vagina rather than in the bladder. Many Task Force members felt that pelvic pain was too broad a term and would not only confuse volunteers, but also exclude many with IC.

Another issue concerned how to exclude patients with diseases that can cause IC-like symptoms without relying on self reports. For example, could a simple urinalysis rule out most of these patients.

Task Force members agreed that the 1987 NIDDK criteria for IC were too exclusive for an epidemiological study; that is, although they were highly specific, they were not very sensitive and consequently excluded too many patients. Several Task Force members also expressed concern that the modified criteria being used in current NIDDK studies are also excluding too many patients to get accurate prevalence data.

The pros and cons of symptom-based population studies versus physician-diagnosed research were also discussed. A criticism of population-based studies was that they were reporting prevalence of symptoms not prevalence of a diagnosis. Identifying participants in a population-based study who have IC-related symptoms does not mean they have IC.

A criticism of studies that relied on physician diagnosis was that they did not have representative samples because most patients who were studied were white and had access to health care. In addition, not all physicians are familiar enough with IC to make a diagnosis, and some may not want to get involved with a chronic illness, particularly with disadvantaged patients.

Dr. McKinley was asked about response rates for the BACH study. He said that response rates are improved when investigators stay in touch with patients through holiday and birthday greetings. BACH investigators are doing that, and the response rates are 80 percent to 85 percent.

Task Force members were impressed with the study design used in the CDC's CFS study, but were concerned about the cost. Dr. Reeves said that a population-based study provides a better sample of socioeconomic levels than clinic-based studies. Studies of HMOs are not population-based because results can only be inferred to the HMO under study. He explained that he also recommends population-based studies for chronic diseases such as CFS and IC rather than clinic-based studies because he believes that some physicians are reluctant to get involved with chronic diseases, especially with disadvantaged patients. Lack of access to health care at lower socioeconomic levels is a problem with clinic-based studies.

Dr. Ratner asked Dr. Reeves to comment on whether a national study of IC was possible and whether data from regional studies such as the CDC's Georgia CFS study and urban studies such as the CDC'S Wichita CFS study could be extrapolated to the national level. Dr. Reeves replied that they could not be extrapolated without some corrections. However, he also said a national population-based study is logistically difficult to do because in addition to a telephone interview, which would not be a problem, patients selected for the study would have to receive a standardized clinical evaluation, which is not possible outside study centers. "Twenty-five percent to 30 percent of people who come into the clinic will have another disorder such as lupus, hypertension, undiagnosed diabetes, or bipolar disorder and that is not a trivial number," he said. Strategies exist to do this type of national study, but they are not cost-effective or feasible.

Dr. Reeves suggested that perhaps the CDC and the NIH could collaborate in future studies that require epidemiological surveys. In the case of CFS, the NIH and CDC have begun to do that, he said, and there are possibly other areas where both organizations could combine strengths.

Breakout Groups

The Task Force divided into two breakout groups, Orange and Red, and adjourned to separate rooms for a working lunch and discussion of several topics prepared in advance and developed to help members focus on research issues regarding the definition of IC, questions for epidemiological and other studies, and appropriate methodologies. When the Task Force reconvened, the two groups reported the following responses to the outline of questions:

Range of normal for urinary frequency, urgency, and nocturia

Orange: There is currently no specific "cut-point" between "normal" and "abnormal." Distributions previously observed should be examined. More data is needed from "normal" populations. The degree of bother needs to be assessed. Survey questions on urgency, frequency, and severity could be adapted from the IPSS or from the AUA's Symptom Index. The International Continence Society (ICS) definition of urgency as "the complaint of a sudden compelling desire to pass urine, which is difficult to defer" should be used. The study should ask subjects whether nocturia is present and how often it occurs. The distribution should be examined. There are no hard and fast limits as to the normal number of voidings per night.

Red: Frequency, urgency, and nocturia should be used for a definition of IC and for screening subjects. The definition should also include the degree of "bothersomeness." Twenty-four-hour voiding diaries of subjects who are well could be compared to those of subjects who are unwell to provide the best estimates for the range of normal. Another important research issue is how the number of voidings per day vary by gender and age. The NOBLE study is the best methodology for this type of study. Standards should not be set in advance.

Range of normal for bladder capacity

Orange: Data on functional bladder capacity, including voiding diaries, should be obtained.

Red: Urodynamics are not required. The largest volume recorded in a 24-hour voiding diary would be sufficient.

Range of normal for bladder cystoscopic findings with and without hydrodistention

Orange: Data from cystoscopy with or without hydrodistention should be obtained.

Red: Cystoscopic examination of subjects in a large population-based epidemiological study of IC would be difficult to achieve; therefore, cystoscopy of any type should not be required for inclusion in studies. However, members of the group disagreed as to whether cystoscopy is useful in making a definitive diagnosis. The group agreed that a cystoscopy is useful in determining treatment strategies and is necessary when a patient has a high risk profile for bladder cancer. Cystoscopy, in addition to other tests, would be useful in a long-term, follow-up study.

Range of normal for urodynamics

Orange: If available, urodynamic data should be reviewed to diagnose overactive bladder versus IC. An administrative database such as Medicare could be used to examine the use of these procedures.

Red: Urodynamics do not have to be part of the definition of IC. A voiding log is less expensive and provides more important information. A urinalysis (i.e., dipstick and microanalysis) for the presence of white cells should be done on all subjects.

Data to be collected for IC, for potentially similar disorders, and for controls

Orange: The group did not reach consensus on whether or not the study should collect data on conditions that are similar to IC or what questions should be used for "screening" entry into studies. However, the breakout group did agree that survey questions about pain should be restricted to pain that originates in the bladder. Because resources are limited, similar conditions probably should not be included in a study of IC.

Red: Data on similar conditions would be useful; however, collecting this data would be expensive in a population-based study. In a patient-tracking follow-up study, collecting data on detrusor instability and non-compliant bladder filling would be useful for determining whether or not these are predictive factors for IC.

Definition of IC for epidemiological studies in 2004 (Is there a gold standard?)

Orange: There is no gold standard. Although a definition is needed for an RFA, this breakout group had no consensus on what the definition should be. It is likely that it will probably be a modification of the ICS definition to include PBS.

Red: If there is a gold standard for the definition of IC, it is symptoms. An epidemiological study should focus on whether or not symptoms become chronic over time after exclusions. Parsons' Pelvic Pain Urgency Frequency (PUF) index could be used as a screening tool and then exclusion criteria could be applied. The group had an enormous difference of opinion over whether or not the term interstitial cystitis distracts from the definition and whether or not it should be changed to PBS. IC is not a disease of the bladder interstitium. In addition, IC is often confused with bacterial cystitis. Because this is a term recognized in the medical literature it would be too confusing to change it but perhaps IC should be coupled with chronic pelvic pain (e.g., IC/CPPB) and eventually IC could be dropped.

Role of biomarkers in defining IC and as an adjunct to epidemiological studies

Orange: The role of biomarkers is critical. Antiproliferative factor should be studied.

Red: Biomarkers should not be part of an epidemiological study. They should be included in later studies, for example, a case-control study.

Minimum duration of symptoms to be included as a case

Orange: The minimum duration of symptoms should be four weeks. This will provide information about early onset of the illness and exclude bladder infection. To avoid inclusion of too many non-cases, the BACH study should be used as a model to permit balance of symptom duration in the study population. Patients should be followed to determine what percentage of IC patients go on to develop chronic illness.

Red: Determining what happens during the first six months or year is important. For example, it is important to know when the odds ratio for getting better changes. To determine this and other important information, patients should be studied as early in the condition as possible. However, because the possibility of infection needs to be ruled out, most likely it will be difficult to get study participants who have duration of symptoms for less than four weeks.

Studies of related entities (e.g., chronic pelvic pain in men, idiopathic pelvic pain in women, and dyspareunia) and subgroups

Orange: Because of limited resources, only those persons who have bladder pain should be studied. Subgroup studies should include ulcerative versus non-ulcerative IC, male IC patients versus female IC patients, newly diagnosed patients, and race and ethnicity. It is difficult to recruit enough children for a study; however, it would be desirable if they could be included.

Red: Studies are needed to determine whether or not ulcerative IC and non-ulcerative IC are two separate disorders. Studies should also include the entire age range of adults. Subgroup studies on race and ethnicity and socioeconomic status of IC patients are also needed. Children should not be studied because of the difficulty of getting enough numbers. Information from the natural history studies can be used to determine what happens in children.

Basic epidemiologic questions regarding IC and chronic pelvic pain in the bladder

Orange and Red: Studies to determine prevalence and incidence are needed.

Natural history of IC and chronic pelvic pain of the bladder (symptom fluctuation, progression and remission of disease, progression/remission of initial onset of culture-negative pain and frequency)

Orange: Studies of the natural history of IC are necessary and should include day-to-day and long-term fluctuation of symptoms, symptoms that move in tandem (database study), progression of disease (to identify chronicity), remission of disease, and progression/remission of initial onset of culture-negative pain and frequency. It is important to determine when and how often IC becomes a chronic problem, if and when it goes into remission and how often, and how long remissions usually last.

Red: Determining the natural history of IC is a priority. For example, is the condition progressive? How fast does it progress? Does it plateau? When does it become a chronic problem, and how often does this occur? How common is remission? Is remission an appropriate term? Does the disorder ever go away? Although relief does occur, patients—at least those who are prevalent—never report being cured. Fluctuation of symptoms should be studied for three-month intervals. It is not necessary to study day-to-day symptom fluctuation.

Risk factors for developing interstitial cystitis/chronic pelvic pain of the bladder

Orange: Determining risk factors is essential. Methodological issues to consider are as follows: long duration between onset of symptoms and diagnosis (one possible approach is to study "early" cases), symptoms leading to changes in behavior rather than the opposite (a prospective study design is essential to determine this), and spectrum of disease (e.g., mild to severe; how quickly symptoms came on). Onset of symptoms and signs must be characterized.

Red: Risk factors such as age, gender, hormonal status, allergies, medications, history of UTI, and diet need to be determined. In addition, there is some evidence that a genetic predisposition is present. Study designs need to consider the long duration between onset of symptoms and diagnosis.

Independent association of IC/CPPB with other diseases, such as allergies, autoimmune diseases, connective tissue diseases, and other diseases

Orange: Yes, this should be studied.

Red: Yes. In addition, a whole host of gynecological symptoms such as endometriosis, yeast vaginitis, and vulvodynia should be studied because they are associated with IC or diagnosed in place of IC.

Types of studies that will best answer these questions

Orange: Several types of research studies are needed to answer all the questions that have been raised about interstitial cystitis. Population-based, cross-sectional studies like BACH are excellent and are needed to determine the prevalence of symptoms that define the disease as well as other chronic pelvic pain syndromes. A blend of studies could be useful. A large number of people should be surveyed to identify possible subjects who would then be brought into clinic-based studies. National prevalence of IC/PBS needs to be determined. Studies need to specify the precision of these estimates. Cross-sectional study design has limitations. Prospective studies are needed to learn about risk factors for incidence cases. Physician-diagnosed cases vs. self report of symptoms are challenges in determining the incidence of disease. Economic impact and quality of life (social injury/damage) should be assessed. A longitudinal cohort study with a sample of patients from clinicians' offices should be established to examine (1) definitions of IC used by clinicians and (2) how patients are treated. Questions about IC should be added to ongoing surveys such as the National Health and Nutrition Examination Survey (NHANES). The Urologic Diseases in America (UDA) should assess administrative databases for information relative to IC/PBS.

Red: Population studies such as BACH, combined with clinical (urologic and gynecologic) evaluation, are needed. A group of intensively studied patients could be derived from a population study. Further studies of subgroups would then be conducted. A small study should be conducted with longer follow-up of those who reach a certain threshold of symptoms. Perhaps another ICDB study with controls, preferably matched in some manner, and a longer follow-up study should be conducted. A case-control study could be a subset of a population study. Although it is too early to recommend a registry, this would be very helpful, particularly if it were available to all researchers. A registry could be the outcome of one or more population studies. A major problem is cases lost to follow-up. A great deal of effort needs to be put into ensuring follow-up. The Task Force should consider piggy-backing onto one or more of the National Center for Health Statistics (NCHS) surveys, such as the State and Local Area Integrated Telephone Survey (SLAITS), the National Health Interview Survey (NHIS), and the National Immunization Survey (NIS).

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Attachment: NIDDK Criteria for IC Studies 1987-1988

NIDDK Initial Criteria for IC Studies (1987)

- Automatic diagnosis: Hunner's Ulcer
- Positive factors (need 2):
  — Pain on filling, relieved by emptying
  — Pain (suprapubic, pelvic, vaginal, perineal)
  — Glomerulations on endoscopy
  — Decreased cytometric compliance

NIDDK Revised Criteria for IC Studies (1988)

- Presence of both bladder pain or urinary urgency; glomerulations or Hunner's ulcer
- Exclusions:
  — Cystometric (awake) capacity > 350 mL
  — Using fill rate 30-100 mL/min, absence of intense urge to void at 100 mL gas or 150 mL liquid
  — IVC on cystometry
  — Awake frequency < 8/day
  — No nocturia
  — Duration < 9 mo.
  — Age < 18 yr.
  — Cystitis (bacterial, chemical, TB, XRT)
  — Prostatitis, vaginitis
  — Bladder, uterine, cervical, vaginal, urethral cancer
  — Active herpes
  — Bladder or lower ureteral calculi
  — Urethral diverticulum