DISCUSSION FOLLOWING DR. KRIEGER'S PRESENTATION

Daniel A. Shoskes, MD (Weston, Florida): You made a strong point about tertiary referral and bias. Of the men who are entering the Chronic Prostatitis Collaborative Research Network study or coming to your clinic, what proportion have never had antibiotic therapy?

John N. Krieger, MD (Seattle, Washington): Many patients have previously seen between 1 to 5 practitioners and have had antibiotics before. The standard practice is to give the patient an antibiotic and then examine him if he does not get better.

Dr. Shoskes: Presumably then, most of those who got better when given antibiotics do not come to see you.

Dr. Krieger: I cannot speak to the proportion of patients who are given antibiotics by their primary care practitioner and who get better. I do not have the mechanisms to capture those data. I am not suggesting that the patients I see represent an appropriate sample for an epidemiologic study.

Anthony J. Schaeffer, MD (Chicago, Illinois): Then perhaps there could be a population of men with prostatitis who go to their primary care doctor, respond to a course of antimicrobial therapy, and never make it to a severe chronic disease state. That is a different issue, right?

Mark S. Litwin, MD, MPH (Los Angeles, California): Right. It is a separate group of patients. In order to establish the prevalence or incidence of the disease, you do have to use a true population. However, that may or may not be the focus of a given study. An effort to understand pathophysiology, for example, does not have to be a population-based study. In a study to establish what the most common symptoms are among the numerator of patients in whom we diagnose this disease clinically, again, you do not have to have the denominator of all patients with the condition.

Michel Pontari, MD (Philadelphia, Pennsylvania): The 16S ribosomal findings represent evidence of infection at any time, correct? The ribosomal data are historic, not viable?

Dr. Krieger: Yes. There is an unresolved issue of how long the DNA can last after infection.

Dr. Schaeffer: There are unequivocal data that normal prostates are sterile. Hochreiter *et al.*,[1] using polymerase chain reaction technology, have looked at the prostates of organ donors, and there were no bacterial 16S ribosomal sequences. If you find bacteria in these patient populations, then it is noteworthy that apparently normal people, at least in that organ donor population, did not have evidence of bacteria in the prostate.

Robert B. Nadler, MD (Chicago, Illinois): Is the 16S ribosomal subunit the same for *Escherichia coli*, *Pseudomonas* species, and others? If you find the 16S subunit, then you know that it is from bacteria?

Dr. Krieger: Yes. It is quite easy to tell a human ribosome from a bacterial ribosome. However, not all laboratories can do this analysis because the problem with contamination is huge. You can have positives in sterile surgical instruments. Keay *et al.*[2] have found many positive findings just by assaying some biopsy forceps. They did a similar assay on the instruments and found many of those were positive.

Dr. Shoskes: Just as it can be misleading to equate inflammation with the presence of leukocytes, it can be misleading to use the terms *infection* and *bacterial presence* interchangeably. The data that you have shown would suggest that a higher proportion of men with chronic pelvic pain syndrome have bacteria present in the prostate. You touched on the hypothesis that this might indicate a true infection, or it might be an epiphenomenon in that something changes in the environment to allow the bacteria to grow. Another possibility is that the organism is an initial stimulus for a subsequent immune response. How do you define infection and how do you differentiate infection from colonization in these patients?

Dr. Krieger: Of the 2 issues that you are raising, one is viability, and that is an area of intense debate among bacteriologists today, especially when you cannot culture most organisms. The other point is, how do you satisfy Koch's postulates for a disease process to say that this pathogen causes this disease. People now are trying to define that in molecular terms. The bottom line is that you cannot do it with any single method or with a cross-sectional study. The data I have shown do not establish this bacterial presence as a cause of the disease. Moreover, the evidence for infectious causes varies dramatically from disease to disease.

Dr. Nadler: Just because you see the 16S ribosomal subunit in there does not mean the prostate was colonized. It just means that there was a time when there were some bacteria in the prostate.

Dr. Schaeffer: Right. Colonization would imply the bacteria are alive. We could go through the different steps in the reasoning. Using polymerase chain reaction technology, Hochreiter *et al.*[1] have shown, in a small number of organ donors, that you find nothing in the prostates of men who were presumably healthy. Then, you have a group of men who have culturable uropathogens localized to the prostate. In our cohort study it is about 7%. Then the question would be, are those bacteria involved in a disease process, or are they just there.

Dr. Shoskes: We found >60% presence of bacteria, which could be colonization or infection.

Dr. Schaeffer: It is all bacteria. We framed it in terms of pathogens that have been known to cause disease in the urinary tract. But even in those patients who are colonized, who have positive cultures with *E. coli*, the question becomes whether those pathogens are causing the problem. The correlate is the man with chronic bacterial prostatitis. Does that man come in your office because of pain and discomfort in the pelvis or because of acute urinary tract infection?

Jackson E. Fowler, Jr., MD (Jackson, Mississippi): If you have a patient with chronic bacterial prostatitis and a culture positive for *Pseudomonas*, then you treat him with antibiotics. Uniformly, these individuals are asymptomatic a year later, despite the fact that you can still isolate that organism. I think it is a quantum leap to say that organisms usually considered nonpathogenic are causing all these symptoms, when we know that patients who have infections by established pathogens are asymptomatic if their bladder and urine are sterile.

Dr. Schaeffer: That is the other side of the argument. I think what we are trying to do here is lay out a broad spectrum of concepts. The traces of bacterial presence do not establish the organism as a pathogen. So despite whether the bacteria are there or not or whether you know how many are there, you have to demonstrate by one means or another that the organism is a pathogen.

Dr. Shoskes: It is either a pathogen for an infection or an instigator for an immune response.

Dr. Krieger: A bit of evidence worth noting is that patients with evidence of microbial DNAs are statistically more likely to have leukocytes in their expressed prostatic secretions.

REFERENCES

1. Hochreiter WW, Duncan JL, and Schaeffer AJ: Evaluation of the bacterial flora of the prostate using a 16S rRNA gene based polymerase chain reaction. J Urol **163:** 127–130, 2000.

2. Keay S, Zhang CO, Baldwin BR, *et al:* Polymerase chain reaction amplification of bacterial 16S rRNA genes from cold-cup biopsy forceps. J Urol **160:** 2229–2231, 1998.