



# The Dysuria-Pyuria Syndrome

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## THE DYSURIA-PYURIA SYNDROME

MOST clinicians immediately suspect a diagnosis of bacterial cystitis in a woman who has dysuria and frequent urination but no clinical evidence of upper-urinary-tract infection. Yet studies from the United Kingdom<sup>1-3</sup> and the United States<sup>4</sup> show that 30 to 50 per cent of women seeking primary care for these symptoms do not have a positive urine culture according to the traditional criterion: isolation of a presumed pathogen, in pure culture, in concentrations of  $>10^5$  bacteria per milliliter of urine in a clean-voided specimen. We have reported one reason for this phenomenon<sup>4</sup>: dysuria may often represent a vaginal, not a urinary-tract, infection. However, even when vaginitis has been carefully ruled out, there are still many symptomatic women in whom urine cultures are reported as negative. Such patients are sometimes told that "there is nothing wrong." Investigators have suspected that something was wrong — possibly infection that is localized to the urethra — and have applied the term "urethral syndrome" to such patients. What is the cause of this syndrome? Can the diagnosis be made by positive findings, rather than by exclusion? What are the implications for therapy?

In this issue of the *Journal*, Stamm and his colleagues in Seattle provide some interesting answers to these questions. Their first valuable contribution is to establish that many patients (46 per cent) have a bacterial infection, despite the "negative" culture. By obtaining suprapubic aspirates and thus avoiding contamination of the urine, they found that women with the urethral syndrome often have bacteriuria but with fewer than  $10^5$  bacteria. These patients have the same clinical characteristics as patients with  $>10^5$  bacteria, and they have the same organisms: predominantly *Escherichia coli* and occasionally other coliforms and *Staphylococcus saprophyticus*. It seems unlikely that inflammation is restricted to the urethra, since the frequent hematuria and suprapubic pain suggest inflammation of the bladder wall as well.

The finding of low-count bacterial infection requires a reexamination of the traditional definition of a "positive" urine culture as applied to symptomatic women. It is not widely appreciated that the threshold concentration of  $>10^5$  bacteria per milliliter of urine was based on studies in asymptomatic women. From the outset, however, those who conducted the landmark studies of quantitative bacteriuria recognized that symptomatic women sometimes had lower concentrations of bacteria.<sup>5</sup> The Seattle study confirms this observation and demonstrates that cultures with  $<10^5$  bacteria should not be ignored in symptomatic women.

A second valuable contribution of the Seattle study is the demonstration that *Chlamydia trachomatis* is a causative agent in these patients, as it is in nongonococcal urethritis in men<sup>6</sup> — possibly an analogous condition. Like bacterial infection of the bladder, chlamydial infection is usually associated with pyuria.

Eleven of the 59 patients with "negative" cultures (19 per cent) had chlamydial infections, and 10 of these 11 had pyuria. *C. trachomatis* can be transmitted sexually and has a somewhat different spectrum of antimicrobial sensitivities from that of the coliforms. Thus, it may prove valuable to distinguish chlamydial from bacterial infection.

There were 21 patients in the Seattle study (36 per cent) without pyuria in whom no infectious cause could be found despite careful investigation. *Neisseria gonorrhoeae*, although not found in this study, may have a more important role in other population groups.<sup>7</sup> In a patient with persistent dysuria in sterile cultures, "interstitial cystitis" should be considered; this unusual disorder of unknown cause can be diagnosed by cystoscopy.<sup>8</sup> The role of other bacterial and viral agents in the patients in the Seattle study with apparently sterile urine and no pyuria remains speculative, but it is interesting that two patients in this "uninfected" group had genital herpes simplex.

Thus, the Seattle workers found that women with dysuria and frequent urination but without clinical evidence of pyelonephritis could be divided into four groups: three groups with potentially treatable infections — those with  $>10^5$  bacteria ("cystitis"), those with  $<10^5$  bacteria, and those with chlamydial infection — and one group with no recognized cause.

Although it remains to be demonstrated through controlled trials that patients with  $<10^5$  bacteria or chlamydial infection will benefit from antimicrobial therapy and that patients with no recognized cause will not, we believe it is reasonable to make this assumption pending further information.

How might the clinician use these findings in the diagnosis and treatment of the typical woman who seeks primary care for dysuria and frequent urination — a woman who is young but not pregnant, free of known urinary or other disease, and without symptoms or signs of acute pyelonephritis? The history is of greater value than the physical examination. All patients with dysuria should be asked explicitly about symptoms of vaginal discharge or irritation. According to our studies, "external dysuria" (pain felt in the inflamed vaginal labia as a stream of urine passes) suggests vaginal infection, and "internal dysuria" (pain felt to be inside the body) suggests urinary-tract infection.<sup>4</sup> One should ask whether a recent sexual partner has had urethral discharge or dysuria; if so, a culture for gonorrhea might be more helpful and chlamydial infection more likely. According to the Seattle study, a recent new sexual partner and a longer duration of symptoms appear to indicate chlamydial infection, whereas a history of hematuria and of sudden onset of symptoms seems to indicate low-count bacterial infection.

The findings of Stamm and his colleagues show that urinalysis is of critical importance, because potentially treatable infection was found in 95 per cent of dysuric patients who also had pyuria and in very few

who did not have pyuria. Indeed, it may be useful to speak of the dysuria-pyuria syndrome. Patients with this syndrome would include almost all those with clinically diagnosed cystitis and those with bacterial and chlamydial forms of the urethral syndrome — patients who will or might benefit from immediate antimicrobial therapy. The Seattle group performed the urinalysis by placing uncentrifuged urine in a hemocytometer chamber. This method avoids the delay involved in centrifugation and provides more reliable measurements of pyuria than does the usual examination of white cells in the spun urine sediment<sup>9</sup>; however, the chance to examine the sediment for casts and bacteria is lost.

What is the role of the urine culture in such patients? On the one hand, the distinction between "cystitis" and the "urethral syndrome," which is made according to the urine culture, now seems less important. On the other hand, the result of the culture and antibacterial-sensitivity report is of great value in the few patients who do not respond to the initial antibacterial agent. Furthermore, a substantial fraction of patients without clinical indications of upper-urinary-tract disease have antibody-coated bacteria, as determined by means of a test performed after a urine culture is found to be positive.<sup>10</sup> These patients, who have laboratory but not clinical evidence of disease of the upper urinary tract, may benefit from more prolonged therapy.

If treatment is given before the results of the culture are known, tetracycline or sulfonamides are the most appropriate antimicrobial agents. These drugs are usually active against the predominant bacterial pathogens and also against chlamydia. The efficacy of ampicillin against chlamydia is uncertain.

For those of us who have been perplexed by the urethral syndrome, this study from Seattle provides valuable new information. Clinicians can now give more rational care to the several million women who suffer from this condition each year.

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## VITAMIN E — A RADICAL DEFENSE

SOME view life as "just a bowl of cherries," and others perceive it as a series of attacks by free radicals that ultimately lead to our rancidity. It is for those who share this latter view that the article by Corash and his associates in this week's *Journal* will be of considerable interest.

Free radicals differ from other chemical species in possessing an unpaired electron. Superoxide radicals ( $O_2^-$ ) are produced within cells both by auto-oxidation of reduced electron-transferring components and by enzymatic processes.<sup>1</sup> Their intrinsic reactivity and their ability to generate even more potent oxidants when they interact with peroxides constitute a constant threat to cellular integrity. The superoxide radical serves useful functions — it participates in the bactericidal action of neutrophils and is a mediator of the inflammatory reaction<sup>2</sup> — but when the superoxide radical and its metabolic products go unchecked they can damage membrane lipids and even denature DNA.

Free radicals are continuously generated but are produced in increased quantities after exposure to hyperoxia or ionizing radiation, during phagocytosis, and after administration of certain drugs and chemicals. The interaction of ascorbic acid with inorganic iron results in generation of free radicals.

The human body possesses a number of mechanisms to deal with the potentially damaging effects of free radicals and their metabolic products.<sup>3</sup> The cellular defense mechanisms involve the enzymes superoxide dismutase, glutathione synthetase, glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase, and catalase. Plasma proteins with antioxidant potential include both ceruloplasmin and transferrin. Nutrients also contribute to defense against oxidative stress and cellular damage. Examples include the sulfhydryl-containing amino acids, the minerals selenium, zinc, and copper, and the vitamins riboflavin and tocopherol (vitamin E).

The susceptibility of a given tissue to an oxidative stress is a function of the overall balance between the magnitude of the oxidative stress and its own antioxidant potential. In tissues with a genetic defect in the ability to deal with oxidant stress, the provision of extra antioxidant may prove to be of considerable value.

Vitamin E is the oldest recognized biologic antioxidant. Fifty years after its discovery its precise therapeutic role remains ill-defined, although the list of disorders in which it may be of benefit has slowly grown.<sup>4</sup> Studies describing the therapeutic benefits of vitamin E can be classified into three categories. The first and most readily recognized category is the one in which vitamin E has been used to correct a deficiency state and its associated pathologic abnormalities. Examples include the hemolytic anemia of low-birth-weight infants, the modest shortening of red-cell life span in patients with cystic fibrosis, the hyperaggregability of platelets in patients with biliary atresia, and the retinitis pigmentosa, myopathy, and cerebellar dysfunction of patients with hereditary abetalipoproteinemia.

A second category in which vitamin E has been reported to be of benefit includes conditions in which no deficiency necessarily exists but large doses of the vitamin are employed to counter the effects of prooxidant assault. For example, vitamin E has been used to prevent or reduce the severity of retrolental fibroplasia in premature infants and to lessen the severity of bronchopulmonary dysplasia in infants exposed to prolonged oxygen administration in the treatment of the respiratory-distress syndrome. Vitamin E has also been employed in large quantities to counter the cardiotoxic effects of the chemotherapeutic agent doxorubicin.

The third category in which pharmacologic doses of the vitamin have been employed, with apparent success and again in the absence of a defined deficiency, includes situations in which the antioxidant has been used to compensate for a preexisting defect in the body's defense against free radicals. Among the examples are hereditary hemolytic anemias due to deficiencies in glutathione synthetase and glucose-6-phosphate dehydrogenase and leukocyte dysfunction in patients with a deficiency in glutathione synthetase. Most recently an observation that defies categorization has been reported.<sup>5</sup> In patients with sickle-cell anemia, the administration of 450 U of vitamin E per day for six to 36 weeks was found to cause a substantial reduction in the number of irreversibly sickled cells.

Fortunately, large doses of this vitamin appear to be tolerated with relative impunity; although megavitamin therapy may have side effects, including potentiation of the anticoagulant effect of warfarin and in vitro impairment of the bactericidal capacity of leukocytes.

Corash and his colleagues acknowledge that their observation, although of theoretical interest, is of limited clinical importance in view of the modest increases in hemoglobin produced in subjects with only minimal shortening of red-cell life span. If they can demonstrate that continuous administration of large doses of vitamin E can protect these patients from hemolytic episodes, which are often induced by intercurrent illnesses, or reduce the incidence of hyperbilirubinemia in infants with a deficiency in glucose-