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The mysterious "urethral syndrome"

A rapid and accurate test for bacteriuria would improve its management

Symptoms of dysuria and frequency of micturition (usually, although often inaccurately, labelled cystitis) are common in women, especially in those of childbearing age. Many patients have become disillusioned with doctors' attitude to this condition and so no longer seek their help for it. Official statistics will thus give too low an incidence for such symptoms, which have recently been estimated to affect 2·5 million people a year in the United Kingdom.[1]

Nearly half the women attending general practitioners with dysuria and frequency have a "significant bacteriuria,"[2] indicating urinary tract infection with common bacterial pathogens (for example, *Escherichia coli*, *Proteus mirabilis*, *Staphylococcus saprophyticus*). This usually responds rapidly to antibiotic treatment. The main problem is the aetiology of the symptoms in the other half, whose urine is not infected with these organisms. Although probably inappropriate in a literal sense, the term "urethral syndrome" is used to describe this condition.

Most of the effort put into understanding the urethral syndrome has gone towards establishing possible microbial causes, and many candidates have been suggested—for example, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, herpes simplex (types 1 and 2), *Gardnerella vaginalis*, and *Ureaplasma urealyticum*.[3] Though no doubt exists that these sexually transmitted organisms may cause dysuria and frequency, only a few patients presenting to their general practitioner with these symptoms will be infected with these agents.[4,5]

Two other possible causes of the urethral syndrome have been much debated. Firstly, Stamm and his colleagues have suggested that many patients in whom the urethral syndrome was diagnosed were suffering, in fact, from a bacterial infection but with a concentration of *E coli* in the bladder urine (10^2/ml) well below the 10^5/ml usually taken to indicate significant bacteriuria.[6] Even if this theory was correct, altering the criterion for significant bacteriuria in this way would account for the symptoms in only a further 8·5% of the patients studied.[7] Thus this theory would not fully explain the urethral syndrome. Patients presenting with dysuria and frequency may have low urinary bacterial counts—for example, in very early infections or patients with dilute or alkaline urine. If the diagnosis is in doubt a further examination of urine a day or two later will usually settle the matter, although this delay may not always be acceptable.

Secondly, Maskell and her colleagues have proposed that the urethral syndrome is caused by infection with "fastidious bacteria," so called because they will not grow readily on media used for routine urine culture.[8] These organisms, chiefly lactobacilli (but including streptococci and diphtheroids), live as commensals in the lower genital tract. Elsewhere in the body infections may be caused by organisms of low virulence when they invade damaged tissue[9]; normally harmless bacteria could infect urethral tissue damaged during sexual intercourse.

The hypothesis implicating fastidious bacteria is, however, controversial, and many arguments have been advanced against it.[3] Recently two studies have cast further doubt on its validity. Firstly, Gillespie *et al* isolated fastidious bacteria in no greater numbers from the urine of patients with the urethral syndrome than from the urine of asymptomatic women.[5] They found that the numbers of leucocytes in the urine of patients and controls were similar—further evidence against bacterial infection. Secondly, Cooper *et al* reported that treatment of the urethral syndrome with an antibiotic (co-amoxiclav) active against lactobacilli gave the same "cure rate" as treatment with fosfomycin, which is inactive against lactobacilli.[10] Furthermore, lactobacilli may actually help to prevent urinary infections.[11]

There are many causes of dysuria or frequency other than infections of the bladder or the urethra. The most common of these, occurring in up to one third of otherwise healthy women with acute dysuria, is vaginitis.[12] This is characterised by an external rather than internal sensation of discomfort during micturition. Claims have also been made that factors such as allergies, cold weather, urethral obstruction, abnormal function of detrusor or sphincter muscles, and interstitial cystitis or cystitis cystica may cause dysuria.[12-15] Dysuria may also be secondary to the dry urethral and vaginal mucosae found in postmenopausal women deficient in oestrogen. Psychological factors such as tension and anxiety are important in some patients, as is trauma resulting from intercourse. More than one of these conditions may be present at any one time. Obviously, distinguishing between bacterial cystitis or sexually transmitted infections and the urethral syndrome is important.

The condition is self limiting and seems to do no permanent damage.[4] Inevitably many patients with the urethral syndrome are treated with antibiotics by their general practitioners. Although this practice is unsatisfactory in principle, improving on it would depend on a rapid and accurate test for bacteriuria, which could be carried out in the general practitioner's surgery and give a result within minutes.

Maybe part of the answer to the riddle of the urethral syndrome lies in some micro-organism as yet undiscovered. After all, *Legionella pneumophila*, *Borrelia burgdorferi*, and *Helicobacter pylori* were unknown pathogens 15 years ago.

The urethral syndrome is common and distressing and causes much unhappiness. It inevitably results in the overuse of antibiotics and proliferation of bacteria resistant to antibiotics. It deserves more thorough investigation than it has received in the past.

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Sex hormones, autoimmune diseases, and immune responses

More implications for research than treatment

Autoimmune diseases are far more common in women than in men. For example, the female to male ratio is 9:1 in systemic lupus erythematosus and 4:1 in rheumatoid arthritis.[1] These observations suggest that sex hormones may help to determine this susceptibility. Though some research findings seem to confirm this suggestion, others are more equivocal; and more recent work suggests a much more complex role for sex hormones in autoimmune diseases.

Some of the most suggestive evidence for the influence of sex hormones relates to rheumatoid arthritis. Thus rheumatoid arthritis begins more commonly in the childbearing years, and both the onset of disease and exacerbations are associated with the postpartum period. Pregnancy is also associated with spontaneous remissions and may itself reduce the risk of developing rheumatoid arthritis.[2] Similarly, autoimmune thyroiditis is encountered as a transient postpartum disorder.

There are also interesting animal models of human autoimmune disease whose natural course may be drastically altered by manipulating sex hormone concentrations. NZB x NZW F1 (BW) mice develop progressive and eventually fatal immune complex nephritis and autoantibodies resembling human lupus. Female BW mice, however, succumb to the disease far earlier than male mice. Prepubertal orchidectomy or the administration of oestrogens or progesterone accelerates the renal disease and the resulting mortality in male mice. Conversely, dihydrotestosterone retards progression of disease in female BW mice.[1] Likewise, experimental systemic lupus erythematosus induced in normal mice can be rapidly accelerated by oestrogens and retarded by testosterone.[3]

The practical implication for clinical medicine is that hormonal manipulation may alter susceptibility to autoimmune disease. There is some evidence that oral contraceptives containing oestrogen provoke exacerbations of systemic lupus erythematosus,[4] but the influence of oral contraceptives on susceptibility to rheumatoid arthritis has proved more contentious. Some studies have shown a significant reduction in the incidence of the disease in women using oral contraceptives.[5] For example, among a population attending a Dutch clinic information on contraceptive practice was obtained from 135 young women with rheumatoid arthritis of recent onset and 378 controls with other rheumatic disorders.[6] The risk of developing the disease was found to be significantly reduced by past or present use of oral contraceptives, and protection was greater in women aged 31-40 at the onset of symptoms and with a family history of rheumatoid arthritis. Further analysis suggested that protection was confined to patients with severe forms of the disease; the incidence in women who had used the pill before the onset of symptoms was less than half that in women who had never used oral contraceptives.[7]

These findings were not confirmed in a study of different design in the United States.[8] The incidence of rheumatoid arthritis was determined in a cohort of 121 700 female nurses aged 35-55 who were followed up regularly from 1976 to 1984. Past use of oral contraceptives did not reduce their risk of developing rheumatoid arthritis.

Many factors account for the differing results of such surveys. Some studies have drawn on patients attending clinics and others on normal populations, while methods of collating data and statistical analysis have varied greatly. The chronological order of the reported studies may also have influenced the results as there is some evidence that the incidence of rheumatoid arthritis, particularly its more severe forms, may be declining.[5,9] The influence of postmenopausal hormone replacement is less controversial: there is no evidence that this treatment affects the incidence of the disease.[8,10] Thus doctors may reasonably infer that prescribing female sex hormones is unlikely to affect the risks of developing rheumatoid arthritis. These hormones are also unlikely to affect the clinical course of established disease.

How does the female preponderance of autoimmune diseases illuminate the pathogenesis of these disorders? As immunopathological mechanisms are implicated the greater immune responsiveness of women to conventional antigens might be supposed to be responsible for the sex differences.[1] And at first sight this enhanced responsiveness might seem attributable to sex hormones. Certainly, 17β-oestradiol